Interdisciplinary CardioVascular and Thoracic Surgery 2023, 36(1), ivad003
https://doi.org/10.1093/icvts/ivad003 Advance Access publication 9 January 2023

Cite this article as: Spaans LN, Bousema JE, Meijer P, Bouwman R.(A), van den Broek R, Mourisse J *et al*. Acute pain management after thoracoscopic lung resection: a systematic review and explorative meta-analysis. Interdiscip CardioVasc Thorac Surg 2023; doi:10.1093/icvts/ivad003.

Acute pain management after thoracoscopic lung resection: a systematic review and explorative meta-analysis

Louisa N. Spaans [a], Jelle E. Bousema[a], Patrick Meijer[b], R.A. (Arthur) Bouwman[c], Renee van den Broek[c], Jo Mourisse[d], Marcel G.W. Dijkgraaf[e], Ad F.T.M. Verhagen[f] and Frank J.C. van den Broek[a,*]

[a] Department of Surgery, Máxima Medical Center, Veldhoven, Netherlands
[b] Department of Anesthesiology, Máxima Medical Center, Veldhoven, Netherlands
[c] Department of Anesthesiology, Intensive Care and Pain Medicine, Catharina Hospital, Eindhoven, Netherlands
[d] Department of Anaesthesiology, Pain and Palliative Medicine, Radboud University Medical Center, Nijmegen, Netherlands
[e] Department of Epidemiology and Data Science, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands
[f] Department of Cardiothoracic Surgery, Radboud University Medical Center, Nijmegen, Netherlands

* Corresponding author. Department of Surgery, Máxima MC, PO Box 7777, 5500 MB Veldhoven, Netherlands. Tel: +31-040-8888550; e-mail: optrial.resurge@mmc.nl (F.J.C. van den Broek).

Received 15 October 2022; accepted 6 January 2023

Key question

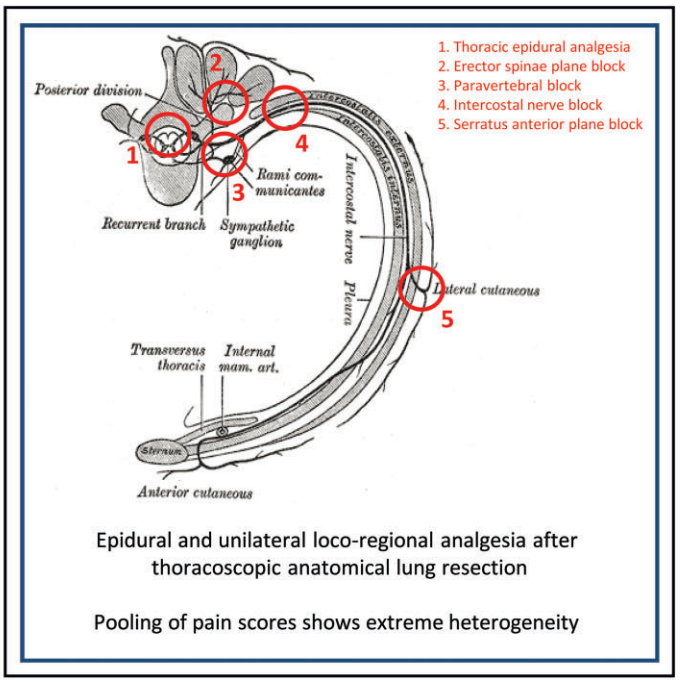
What is the optimal analgesic approach for effective acute pain management in thoracoscopic anatomical lung resection?

Key finding(s)

Exploratory meta-analysis suggests acceptable pain scores for thoracic epidural and unilateral loco-regional analgesia.

Take-home message

Guidelines tend to advocate unilateral loco-regional analgesia as a viable alternative, but high heterogeneity precludes firm conclusions.



Abstract

OBJECTIVES: Pain after thoracoscopic surgery may increase the incidence of postoperative complications and impair recovery. Guidelines lack consensus regarding postoperative analgesia. We performed a systematic review and meta-analysis to determine the mean pain scores of different analgesic techniques (thoracic epidural analgesia, continuous or single-shot unilateral regional analgesia and only systemic analgesia) after thoracoscopic anatomical lung resection.

METHODS: Medline, Embase and Cochrane databases were searched until 1 October 2022. Patients undergoing at least >70% anatomical resections through thoracoscopy reporting postoperative pain scores were included. Due to a high inter-study variability an explorative meta-analysis next to an analytic meta-analysis was performed. The quality of evidence has been evaluated using the Grading of Recommendations Assessment, Development and Evaluation system.

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

RESULTS: A total of 51 studies comprising 5573 patients were included. Mean 24, 48 and 72 h pain scores with 95% confidence interval on a 0–10 scale were calculated. Length of hospital stay, postoperative nausea and vomiting, additional opioids and the use of rescue analgesia were analysed as secondary outcomes. A common-effect size was estimated with an extreme high heterogeneity for which pooling of the studies was not appropriate. An exploratory meta-analysis demonstrated acceptable mean pain scores of Numeric Rating Scale <4 for all analgesic techniques.

CONCLUSIONS: This extensive literature review and attempt to pool mean pain scores for meta-analysis demonstrates that unilateral regional analgesia is gaining popularity over thoracic epidural analgesia in thoracoscopic anatomical lung resection, despite great heterogeneity and limitations of current studies precluding such recommendations.

PROSPERO REGISTRATION: ID number 205311

Keywords: Acute postoperative pain • Pain management • Video-assisted thoracic surgery • Anatomic lung resection • Thoracic epidural analgesia • Regional analgesia • Intercostal analgesia • Health economics

ABBREVIATIONS

CI	Confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICNB	Intercostal nerve block
LOS	Length of hospital stay
NRS	Numeric Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
PONV	Postoperative nausea and vomiting
PVB	Paravertebral block
RCT(s)	Randomized controlled trial(s)
RoB-2	Risk of Bias tool
ROBINS-I	Risk of Bias tool for Nonrandomised Studies for Interventions
SD	Standard deviation
TEA	Thoracic epidural analgesia
VATS	Video-assisted thoracoscopic surgery

INTRODUCTION

Rationale

Thoracic surgery is associated with severe postoperative pain [1]. Effective analgesia and rapid mobilization are important to enhance recovery and prevent postoperative complications [2]. Despite the introduction of video-assisted thoracoscopic surgery (VATS), still 16% of patients report severe postoperative pain in the first 48 h after surgery [3]. Postoperative pain results in administration of systemic analgesics including opioids, prolonged hospital stay, impaired pulmonary function and increased risk of postoperative complications [4]. Additionally, unrelieved pain is associated with decreased patient satisfaction and with the development of chronic pain syndromes [5].

In current clinical practice, thoracic epidural analgesia (TEA) is still considered the standard of care after thoracoscopic lung surgery [6]. When placed correctly, the analgesic effect of TEA is clear, but failure rates of 9–30% have been described, and the awake placement can be stressful for patients [7]. Moreover, TEA is associated with disadvantages such as immobilization, neurogenic bladder dysfunction and hypotension as well as more severe TEA-related complications such as haematomas and infections [7]. Recent guidelines of the Enhanced Recovery after Surgery Society and the European Society of Thoracic Surgeons as well as the recent PROSPECT guidelines suggest the use of loco-regional analgesic techniques for early mobilization and less epidural related side-effects after VATS as one of the key recommendations [2, 8]. The PROSPECT guidelines do not recommend TEA based on a Delphi consensus even though 3 randomized trials all demonstrated lower pain scores and less opioid use after TEA compared to paravertebral block (PVB). The use of TEA is still part of an ongoing debate in designing enhanced recovery after thoracic surgery (ERATS) protocols [9]. A Dutch national survey confirmed strong variability in using regional analgesic techniques, with a majority (69%) still using TEA after VATS anatomic lung resection [10].

Several papers showed safety and effectiveness of unilateral regional analgesic techniques such as paravertebral, intercostal nerve, serratus anterior and erector spinae plane blocks [11–16]. The approach of the analgesic techniques, whether given as epidural analgesia or loco-regional continuous or single-shot, may play an important role in improved recovery after VATS [2]. A meta-analysis on single-injection versus continuous peripheral nerve blockade in a heterogeneous postoperative patient group showed improved pain control, decreased need for opioids and greater patient satisfaction with the continuous infusion technique [17]. Despite this, single-shot analgesic techniques are gaining popularity as they are fast to apply and may be equally effective as catheter techniques, without compromising patient satisfaction [18].

Our aim was to perform an analytical single-arm meta-analysis of acute pain scores for different analgesic approaches after thoracoscopic anatomical lung resection in patients treated by either TEA (group 1), continuous regional analgesia (group 2), single-shot regional analgesia (group 3) or systemic analgesia only (group 4). In case of large inter-study variability leading to unacceptable heterogeneity, we aim for an exploratory meta-analysis. This approach characterizes individual studies on likely factors that might explain the variation in effect size [19].

MATERIALS AND METHODS

We adhered to PRISMA 2020 checklist (Supplementary Material, Appendix H).

Protocol registration

PROSPERO database: ID number 205311, registered 20 September 2020.

Eligibility criteria

Clinical (non) randomized trials (all included clinical trials published after 1 January 2019 were prospectively registered in a national or international clinical trial database) or observational studies including adults undergoing thoracoscopic (either robotic or conventional) anatomical lung resection [pneumonectomy, (bi)lobectomy and/or segmentectomy] receiving postoperative analgesia through TEA, continuous or single-shot unilateral regional nerve blocks or systemic analgesia.

Search strategy

Studies were identified through electronic search of the Medline (PubMed platform), EMBASE and Cochrane databases on published literature without calendar year or language restrictions. In addition, reference lists of included studies as well as of meta-analysis and systematic reviews related to analgesia after thoracoscopy were scanned for additional relevant studies (citation tracking) [17, 20–22]. The last search was conducted on 1 October 2022. The full search strategy is provided in Supplementary Material, Appendix A.

Study selection

Two authors (L.N.S. and J.E.B.) independently screened the titles and abstracts and if the article fulfilled the inclusion criteria, the same 2 authors read the full-text articles. The inclusion criteria were studies performing thoracoscopic procedures with at least 70% of patients undergoing anatomical lung resection, at least 20 patients per analgesic technique and studies reporting absolute pain scores. The PRISMA flow diagram is shown in Fig. 1. Studies reporting on a population undergoing thoracotomy only were excluded, whereas combined thoracoscopy and thoracotomy populations were included to analyse the thoracoscopic subgroup only. The corresponding authors of studies with insufficient data presentation (only graphic pain scores without absolute pain score values, no pain scores or unknown proportion of anatomical lung resections) were contacted. Three authors responded with absolute mean pain scores [23–25] and 1 author responded with number of anatomical resections [26] and were included in the meta-analysis. Any disagreement in the selection process was resolved by the senior author (F.J.C.v.d.B.).

Primary outcome measures

The primary outcome measure was the mean [standard deviation (SD)] pain score at 24 h after surgery [i.e. Visual Analogue Scale,

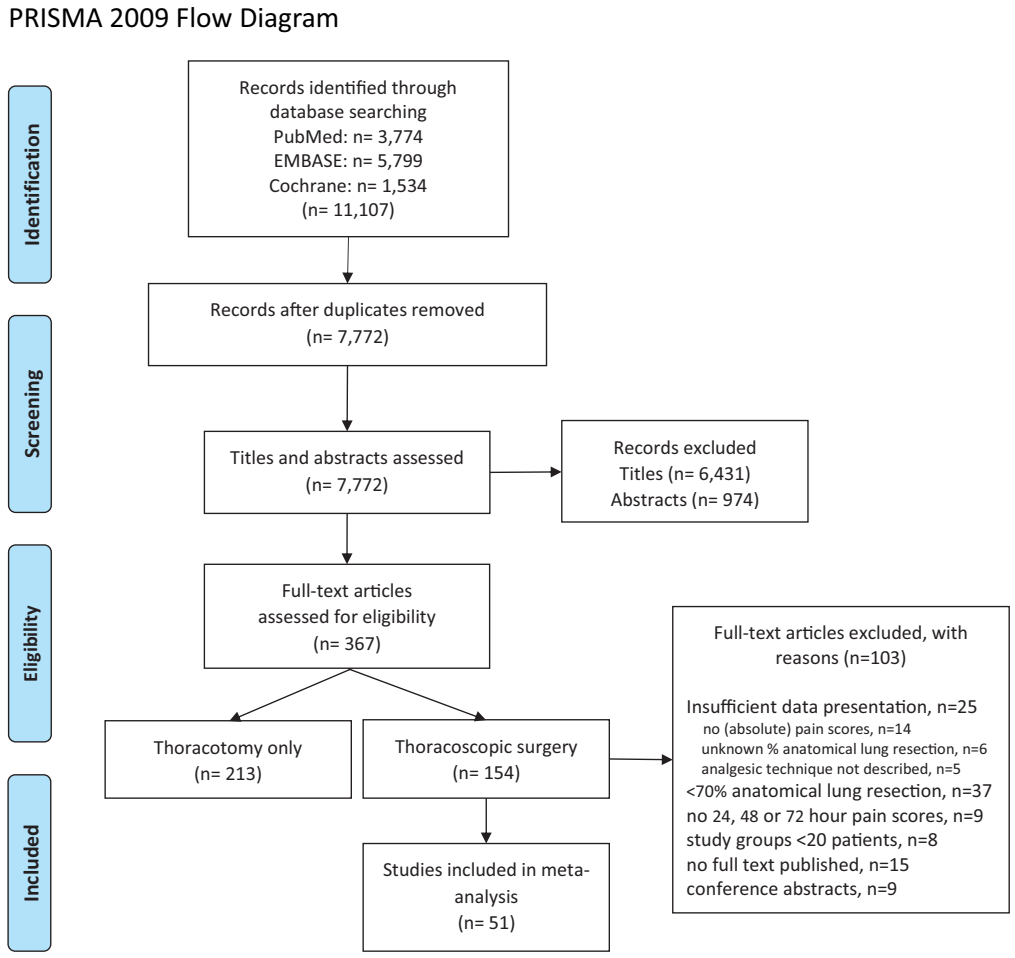


Figure 1: Flow diagram of study selection (*n* = number).

Numeric Rating Scale (NRS) or Verbal Rating Scale). A substantial number of studies reported pain scores as medians. We used validated methods to convert medians to means to complement our meta-analysis with as much available data as possible [27, 28]. If by performing the transformation the data remained skewed, the study subgroup was excluded [28].

Secondary outcome measures

Secondary pain score measure. Also pain scores at 48 and 72 h were registered when available.

Length of hospital stay. The length of hospital stay (LOS) was defined as full calendar days the patient remained in the hospital after surgery (Supplementary Material, Appendix E). If the number of days was reported as (non-skewed) medians, then the medians were converted to means.

Complications related to the analgesic technique. All studies were thoroughly searched for reported complications and adverse events related to the analgesic techniques to report them as secondary outcome measures. The most reported adverse event was postoperative nausea and vomiting (PONV). PONV was mostly reported as the number of patients suffering from PONV and analysed as the proportional incidence of PONV per analgesic group (Supplementary Material, Appendix E). Next to PONV, urinary retention and hypotension (Supplementary Material, Appendix G) were compared between the different analgesic groups. Other block-related complications such as haematomas and infections did not occur. The absence of specific complications was only considered if the article specifically mentioned the complication was absent.

(Additional) opioids. All (additional) opioids that were part of an analgesic technique (multimodal analgesic regimes) were considered, independently from the route of administration: including epidural, systemic or orally given opioids. These were reported as frequency of boluses in the case of patient-controlled analgesia or as total amount of morphine or fentanyl use in 24 h. Fentanyl (1:300), oral (1:1.5) and intravenous (1:3) oxycodone and intravenous morphine (1:30) dosages were converted into Morphine Milligram Equivalent according to the Opioid Conversion Table (Supplementary Material, Appendix F).

Rescue analgesia. Rescue analgesia is defined as analgesic medication given for intermittent breakthrough pain (in different protocols defined as NRS > 3 or NRS > 4). Since non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are used together for rescue analgesia, we did not make an estimation of milligrams used as we did for additional opioids. For the rescue analgesia, we found it more clinically relevant to define the number of patients per analgesic group (incidence) using rescue analgesia as this gives an estimation as to how many patients had unacceptable pain (Supplementary Material, Appendix E).

Data collection

A data collection form was developed to extract relevant information from each included study. Baseline data were extracted per study (Table 1).

Data analysis

We divided all included studies into 4 categories depending on the type of analgesic approach: TEA; continuous unilateral infusion of loco-regional analgesia; single-shot loco-regional analgesia; or only systemic analgesia. We intended a single-arm meta-analysis to evaluate the outcome measures for each analgesic approach, but in case of large heterogeneity between the included studies, we would shift to an exploratory meta-analysis to explain why the effect sizes vary (what are the characteristics of the studies which account for the observed differences) instead of determining whether the treatment has an effect.

Descriptive variables were analysed by using the Statistical Package for Social Sciences for Windows (version 22.0, IBM, Armonk, NY). Continuous data were reported as medians and interquartile range (IQR) and/or total range (non-parametric data) or as means and SD and/or total range (parametric data). Medians and IQR or medians and range were converted into means using the method by [29] and [30]. In case of skewed medians, transformation was not possible. We then back-transformed the results and performed a random-effects model meta-analysis according to the DerSimonian and Laird method and using the *metamean* package in R (version 4.1.2). We performed a sensitivity analysis of 3 different approaches of pooling the studies: studies reporting only means, only medians and a 3rd analysis with means and non-skewed medians transformed to means (Supplementary Material, Appendix I). As no significant clinical difference was shown and the heterogeneity remained high in all analysis, we decided for the third analysis with the most data. We calculated I^2 statistics with 95% confidence interval (95% CI), presenting the percentage of variability that is attributable to between-study heterogeneity. We used I^2 value of >50% as the cut-off indicating significant heterogeneity between studies [31]. An evaluation of the risk of bias was performed by using the Risk of Bias tool (RoB-2) for randomized studies and the Risk of Bias tool for Nonrandomised Studies for Interventions (ROBINS-I) for non-randomized studies [32, 33] (Supplementary Material, Appendix B). The quality of the evidence has been thoroughly evaluated and described using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (Supplementary Material, Appendix C, Table S1). The clinical difference in mean for the primary outcome is not well defined and is context specific [34]. Moreover, the analgesic technique groups cannot be reliably compared to each other due to the high between-study heterogeneity. Therefore, the difference in mean, generally used to find statistical difference between 2 means, was not calculated. We selected 6 patient-centred outcome measures that are important for decision-making. A table of evidence has also been added for additional transparency regarding our quality of evidence evaluation (Supplementary Material, Appendix C, Table 2).

RESULTS

Description of studies

A total of 7772 unique studies were identified, of which 51 [14, 23–26, 35–80] were considered in the meta-analysis including 31 randomized trials and 20 retrospective and observational studies (Fig. 1). In the included 51 studies, a total of 103 different

Table 1: Study characteristics

Study (subgroup)	Analgesia	Gender (% male)	Age (mean)	RCT	n total	Anatomic resection	VATS/RATS ports	Risk of Bias		
Report								Selection	Measure	
Thoracic epidural analgesia										
Nomori et al. (1) (2001)	TEA	67%	64	No	33	100%	Multi	😐	🙂	😐
Yie et al. (1) (2012)	TEA	54%	62	No	70	100%	Multi	😐	😐	😐
Nomori et al. (1) (2016)	TEA	57%	67	No	58	100%	Multi	😐	🙂	😐
Kosinski et al. (2) (2016)	TEA	60%	60	Yes	25	100%	Multi	😐	🙂	🙂
Darr et al. (1) (2017)	TEA	42%	62	No	38	74%	Multi	🙂	😐	😐
Bousema et al. (2) (2019)	TEA	35%	63	No	23	70%	Multi	🙂	🙂	🙂
Miyoshi et al (1) (2021)	TEA	41%	67	No	142	100%	Multi	😐	🙂	🙂
Miyoshi et al (2) (2021)	TEA	36%	68	No	140	100%	Multi	😐	🙂	🙂
Yamazaki et al. (1) (2022)	TEA	49%	69	No	70	79%	Multi	🙂	🙂	🙂
Continuous regional analgesia										
Wildgaard et al. (2012)	ICNB	58%	64	No	48	100%	Multi	🙂	🙂	🙂
Hsieh et al. (1) (2016)	ICNB	62%	61	No	39	100%	Single	🙂	🙂	🙂
Jung et al. (2) (2016)	ICNB	63%	61	No	30	100%	Multi	😐	😐	😐
Kosinski et al. (1) (2016)	TPVB	54%	65	Yes	26	100%	Multi	😐	🙂	🙂
Kadomatsu et al. (1) (2018)	TPVB	46%	68	Yes	26	100%	Multi	🙂	😐	🙂
Kadomatsu et al. (2) (2018)	ICNB	54%	65	Yes	24	100%	Multi	🙂	😐	🙂
Bousema et al. (1) (2019)	ICNB	74%	68	No	23	78%	Multi	🙂	🙂	🙂
Taketa et al. (1) (2019)	TPVB	59%	65	Yes	32	100%	Multi	🙂	🙂	🙂
Taketa et al. (2) (2019)	TPVB	61%	68	Yes	33	100%	Multi	🙂	🙂	🙂
Taketa et al. (1) (2019)	TPVB	63%	67	Yes	40	100%	Multi	🙂	🙂	🙂
Taketa et al. (2) (2019)	ESPB	56%	70	Yes	41	100%	Multi	🙂	🙂	🙂
Er et al. (3) (2021)	SAPB	54%	56	Yes	39	100%	Multi	🙂	🙂	🙂
Tan et al. (1) (2021)	ICNB	46%	61	No	26	77%	Single	🙂	🙂	🙂
Chen et al. (1) (2022)	SAPB	59%	56	Yes	33	100%	Single	🙂	🙂	🙂
Chen et al. (2) (2022)	SAPB	67%	57	Yes	33	100%	Single	🙂	🙂	🙂
Deng et al. (2) (2022)	CRIB	43%	53	Yes	30	100%	Multi	🙂	🙂	🙂
Single-shot regional analgesia										
Hsieh et al. (2) (2016)	ICNB	56%	60	No	39	100%	Single	🙂	🙂	🙂
Park et al. (1) (2018)	SAPB	40%	58	Yes	42	100%	Multi	🙂	🙂	😐
Xu et al. (1) (2018)	TPVB	57%	60	Yes	30	100%	Multi	🙂	🙂	🙂
Xu et al. (2) (2018)	TPVB	60%	59	Yes	30	100%	Multi	🙂	🙂	🙂
Bai et al. (1) (2019)	ICNB	49%	58	Yes	53	77%	Single	🙂	🙂	🙂
Bai et al. (2) (2019)	ICNB	49%	58	Yes	51	84%	Single	🙂	🙂	🙂
Bai et al. (3) (2019)	ICNB	49%	58	Yes	53	85%	Single	🙂	🙂	🙂
Gao et al. (1) (2019)	ESPB	50%	56	Yes	30	100%	Multi	🙂	🙂	🙂
Gao et al. (2) (2019)	ESPB	57%	58	Yes	30	100%	Multi	🙂	🙂	🙂
Gao et al. (3) (2019)	ESPB	57%	57	Yes	30	100%	Multi	🙂	🙂	🙂
Wang et al. (2) (2019)	TPVB	31%	56	No	41	87%	Single	🙂	🙂	😐
Wang et al. (3) (2019)	SAPB	41%	56	No	41	93%	Single	🙂	🙂	😐
Baldinelli (1) (2020)	ICNB	30%	65	No	20	100%	Multi	😐	🙂	🙂
Baldinelli (2) (2020)	SAPB	65%	70	No	20	100%	Multi	😐	🙂	🙂
Ciftci et al. (1) (2020)	ESPB	53%	48	Yes	30	100%	Multi	🙂	🙂	🙂
Kang et al. (1) (2020)	TPVB	51%	52	Yes	41	100%	Multi	🙂	🙂	🙂
Lee et al. (1) (2020)	SAPB	52%	68	Yes	23	100%	Multi	🙂	🙂	🙂
Lee et al. (2) (2020)	ICNB	70%	67	Yes	23	100%	Multi	🙂	🙂	🙂
Viti et al. (1) (2020)	SAPB	61%	68	Yes	46	100%	Multi	🙂	🙂	🙂
Yao et al. (1) (2020)	ESPB	38%	56	Yes	37	100%	Multi	🙂	🙂	🙂
Zhao et al. (1) (2020)	ESPB	55%	59	Yes	33	70%	Multi	🙂	🙂	🙂
Zhao et al. (2) (2020)	TPVB	33%	57	Yes	33	70%	Multi	🙂	🙂	🙂
Er et al. (1) (2021)	TPVB	61%	52	Yes	38	100%	Multi	🙂	🙂	🙂
Er et al. (2) (2021)	TPVB	54%	53	Yes	39	100%	Multi	🙂	🙂	🙂
Marciniak et al. (1) (2021)	ICNB	48%	66	No	178	100%	Multi	😐	🙂	🙂
Marciniak et al. (2) (2021)	ICNB	49%	66	No	218	100%	Multi	😐	🙂	🙂
Qiu et al. (1) (2021)	SSB	52%	63	Yes	21	100%	Multi	🙂	🙂	😐
Qiu et al. (2) (2021)	DSB	62%	63	Yes	21	100%	Multi	🙂	🙂	😐
Qiu et al. (1) (2021)	PVB	47%	58	Yes	30	90%	Multi	🙂	🙂	🙂
Qiu et al. (2) (2021)	SAB	45%	56	Yes	29	93%	Multi	🙂	🙂	🙂
Rao et al. (1) (2021)	ESB	47%	56	Yes	32	100%	Multi	🙂	🙂	🙂
Rao et al. (2) (2021)	ESB	46%	56	Yes	33	100%	Multi	🙂	🙂	🙂
Rao et al. (3) (2021)	ESPB	47%	55	Yes	30	100%	Multi	🙂	🙂	🙂
Turhan et al. (1) (2021)	ESPB	54%	53	Yes	35	100%	Multi	🙂	🙂	🙂
Turhan et al. (2) (2021)	TPVB	46%	54	Yes	35	100%	Multi	🙂	🙂	🙂

Continued

Table 1: Continued

Study (subgroup) Report	Analgesia	Gender (% male)	Age (mean)	RCT	n total	Anatomic resection	VATS/RATS ports	Risk of Bias		
								Selection	Measure	
Turhan et al. (3) (2021)	ICNB	53%	52	Yes	36	100%	Multi	🙂	🙂	🙂
Weksler et al. (1) (2021)	ICNB	28%	63	Yes	25	84%	Multi	🙂	😐	😐
Weksler et al. (2) (2021)	ICNB	56%	63	Yes	25	88%	Multi	🙂	😐	😐
Banks et al. (1) (2022)	ICNB	21%	67	No	34	100%	Multi	🙂	🙂	🙂
Banks et al. (2) (2022)	ICNB	39%	67	No	222	100%	Multi	🙂	🙂	🙂
Banks et al. (3) (2022)	ICNB	35%	65	No	46	100%	Multi	🙂	🙂	🙂
Yamazaki et al. (2) (2022)	ICNB	47%	70	No	70	76%	Multi	🙂	🙂	🙂
Yang et al. (1) (2022)	TPVB	54%	54	Yes	28	100%	Multi	🙂	🙂	🙂
Yang et al. (2) (2022)	TPVB	59%	51	Yes	27	100%	Multi	🙂	🙂	🙂
Yang et al. (3) (2022)	TPVB	55%	54	Yes	29	100%	Multi	🙂	🙂	🙂
Yu et al. (1) (2022)	ICNB	40%	53	Yes	184	72%	Multi	🙂	😐	🙂
Yu et al. (2) (2022)	ICNB	36%	54	Yes	186	74%	Multi	🙂	😐	🙂
Yu et al. (3) (2022)	ICNB	32%	52	Yes	184	73%	Multi	🙂	😐	🙂
Zhang et al. (1) (2022)	TPVB	45%	54	Yes	22	100%	Multi	🙂	🙂	🙂
Zhang et al. (2) (2022)	ESPB	50%	54	Yes	22	100%	Multi	🙂	🙂	🙂
Systemic analgesia										
Yie et al. (2) (2012)	PCIA	66%	61	No	35	100%	Multi	😐	😐	😐
Pu et al. (2013)	PCIA	65%	60	No	51	100%	Multi	🙂	🙂	🙂
Andreetti et al. (2014)	CONT	59%	63	No	75	100%	Multi	☹	😐	😐
Yang et al. (2015)	PCIA	47%	59	Yes	36	100%	Multi	🙂	😐	🙂
Dai et al. (1) (2016)	CONT	82%	57	No	66	100%	Multi	🙂	😐	😐
Dai et al. (2) (2016)	CONT	82%	57	No	66	100%	Single	🙂	😐	😐
Jahangiri et al. (1) (2016)	CONT	74%	39	Yes	35	100%	Multi	🙂	🙂	🙂
Jahangiri et al. (2) (2016)	CONT	69%	42	Yes	35	100%	Multi	🙂	🙂	🙂
Jung et al. (1) (2016)	PCIA	72%	63	No	36	100%	Multi	😐	😐	😐
Wang et al. (1) (2016)	PCIA	50%	56	Yes	40	100%	Multi	🙂	🙂	🙂
Wang et al. (2) (2016)	PCIA	50%	54	Yes	40	100%	Multi	🙂	🙂	🙂
Park et al. (2) (2018)	PCIA	38%	58	Yes	42	100%	Multi	🙂	🙂	😐
Liu et al. (1) (2019)	PCIA	54%	63	No	166	100%	Single	🙂	🙂	🙂
Liu et al. (2) (2019)	PCIA	54%	63	No	162	100%	Multi	🙂	🙂	🙂
Wang et al. (1) (2019)	PCIA	39%	55	No	41	93%	Single	🙂	🙂	🙂
Ciftci et al. (2) (2020)	PCIA	50%	46	Yes	30	100%	Multi	🙂	🙂	🙂
Dastan et al. (1) (2020)	CONT	74%	66	Yes	35	70%	Multi	🙂	🙂	🙂
Dastan et al. (2) (2020)	CONT	69%	42	Yes	35	70%	Multi	🙂	🙂	🙂
Dastan et al. (3) (2020)	CONT	71%	40	Yes	31	70%	Multi	🙂	🙂	🙂
Jiang et al. (1) (2020)	PCIA	64%	56	No	50	100%	Multi	😐	🙂	🙂
Jiang et al. (2) (2020)	PCIA	61%	54	No	49	100%	Multi	😐	🙂	🙂
Viti et al. (2) (2020)	PCIA	68%	71	Yes	44	100%	Multi	🙂	🙂	🙂
Hu et al. (1) (2021)	PCIA	56%	67	No	200	100%	Single	🙂	🙂	🙂
Hu et al. (2) (2021)	PCIA	55%	66	No	200	100%	Multi	🙂	🙂	🙂
Li et al. (1) (2021)	PCIA	0%	52	Yes	71	100%	Multi	🙂	🙂	🙂
Li et al. (2) (2021)	PCIA	0%	50	Yes	72	100%	Multi	🙂	🙂	🙂
Deng et al. (1) (2022)	PCIA	36%	58	Yes	30	100%	Single	🙂	🙂	🙂
Zhang et al. (3) (2022)	PCIA	47%	52	Yes	23	100%	Multi	🙂	🙂	🙂

☹: high risk of bias; 🙂: low risk of bias; 😐: moderate risk of bias; CONT: continuous intravenous infusion; CRIB: continuous rhomboid intercostal block; DSB: deep serratus block; ESPB: erector spinae plane block; ICNB: intercostal nerve block; PCIA: patient controlled intravenous analgesia; RATS: robot-assisted thoracoscopic surgery; RCT: randomized controlled trial; SAPB: serratus anterior plane block; SSB: superficial serratus block; TEA: thoracic epidural analgesia; TPVB: thoracic paravertebral block; VATS: video-assisted thoracoscopic surgery.

analgesic subgroups were identified and subdivided: group 1 TEA (9 subgroups), group 2 continuous unilateral regional analgesia (16 subgroups), group 3 single-shot unilateral regional analgesia (50 subgroups) and group 4 systemic analgesia only (28 subgroups). All included studies except 1 have been published after 2012. The meta-analysis comprised 5573 patients of which 5266 (94.5%) underwent an anatomical lung resection. The mean age of included patients was 59 years (SD 10) and 53% were males (Table 1).

Primary outcome: mean pain scores

Mean pain scores at 24 h after surgery were reported in all studies. The mean pain score with 95% CI and heterogeneity (I^2) at 24 h was 1.9 (1.5–2.4; $I^2 = 79\%$) for TEA, 2.0 (1.4–2.8; $I^2 = 95\%$) for continuous regional analgesia, 2.5 (2.3–2.6; $I^2 = 97\%$) for single-shot regional analgesia and 2.9 (2.6–3.6; $I^2 = 98\%$) in the systemic analgesia group (Fig. 2). Mean pain scores at 48 and 72 h after surgery with the respective heterogeneity are provided in Fig. 2.

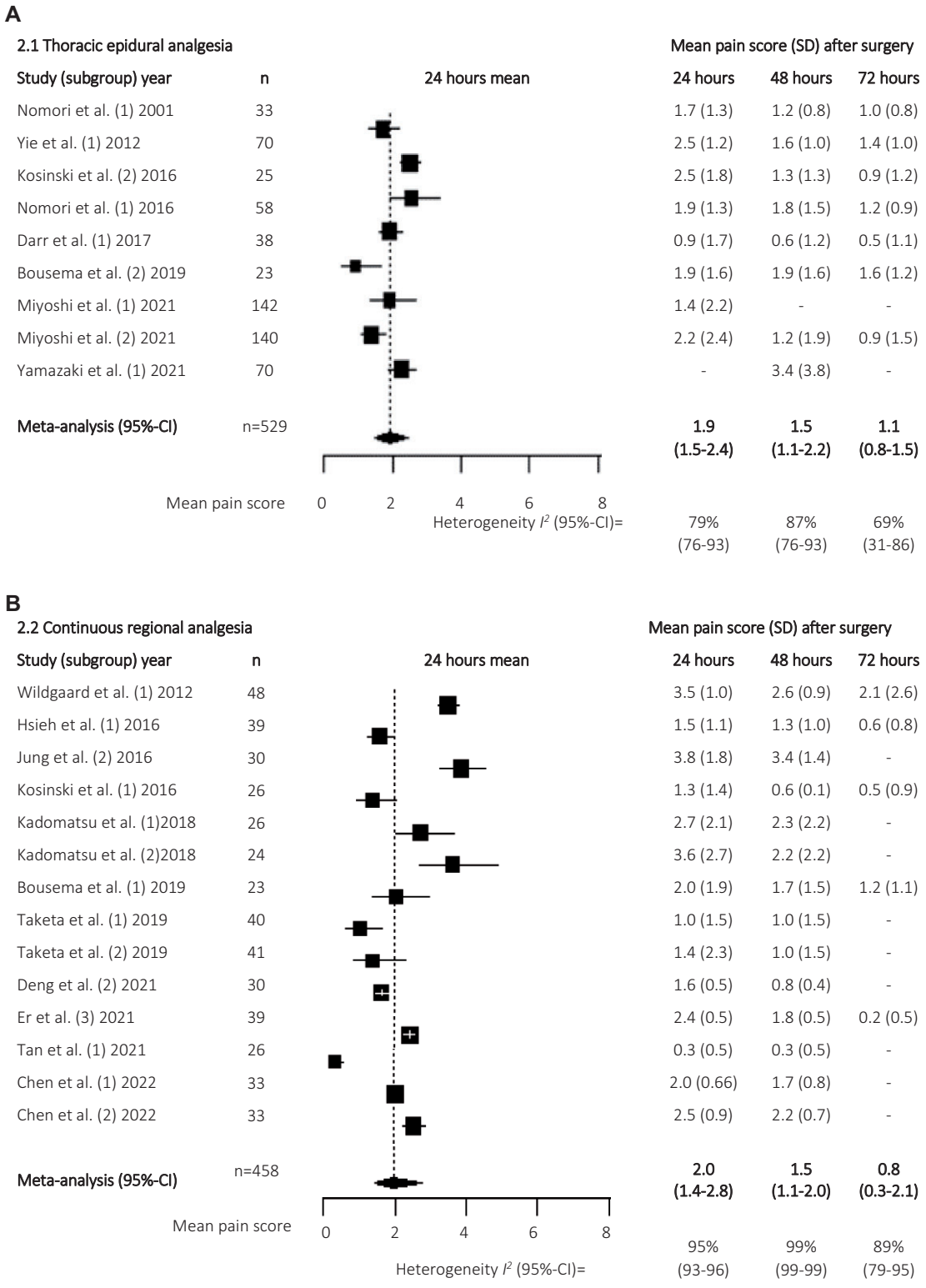


Figure 2: Meta-analysis of mean (standard deviation) pain scores 24, 48 and 72 h after video-assisted thoracoscopic surgery anatomical lung resection. (**A**) Thoracic epidural analgesia. (**B**) Continuous regional analgesia. (**C**) Single-shot regional analgesia. (**D**) Systemic analgesia. 95% CI: 95% confidence interval; *n*: total number of patients; SD: standard deviation.

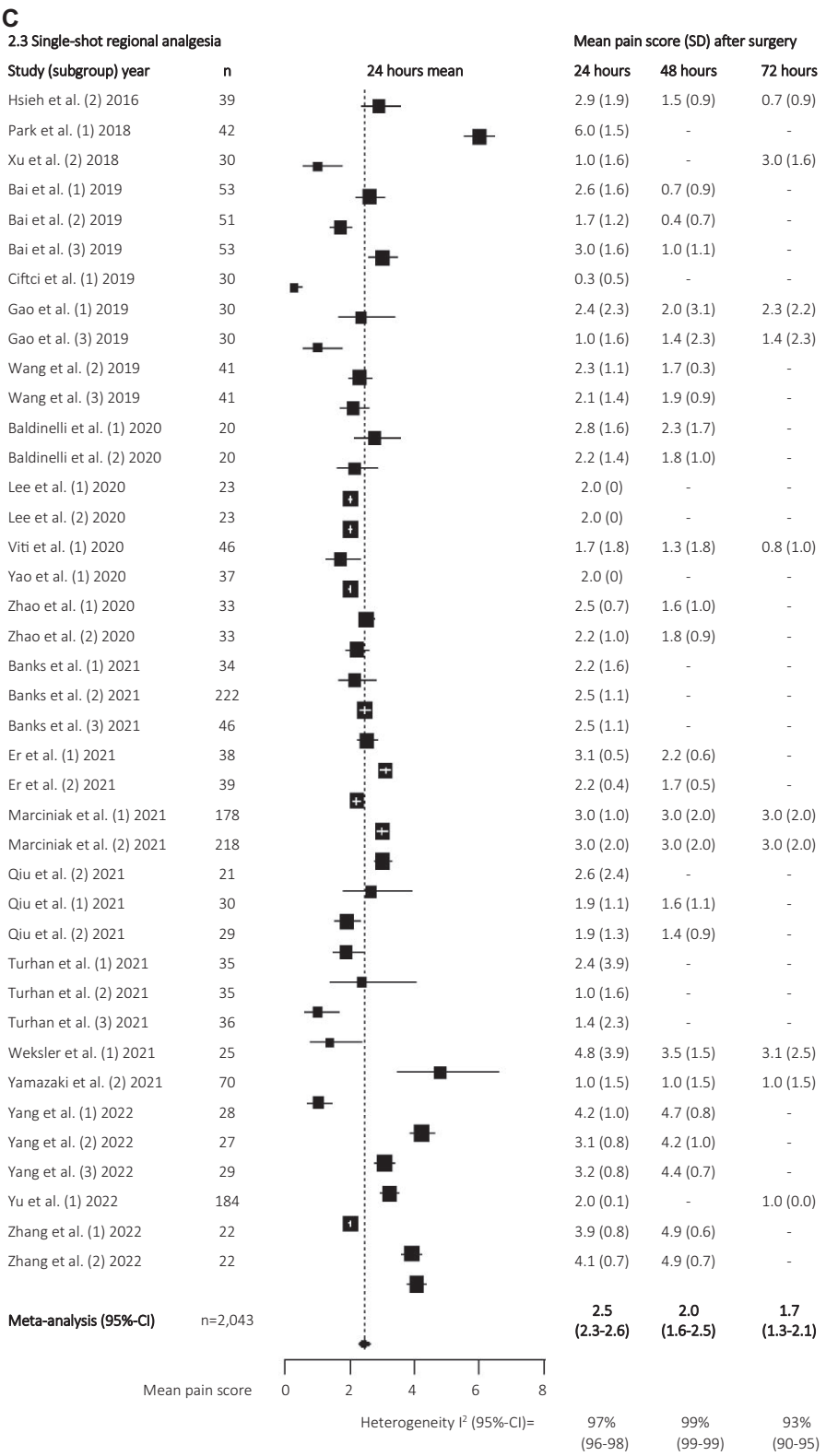


Figure 2: (Continued)

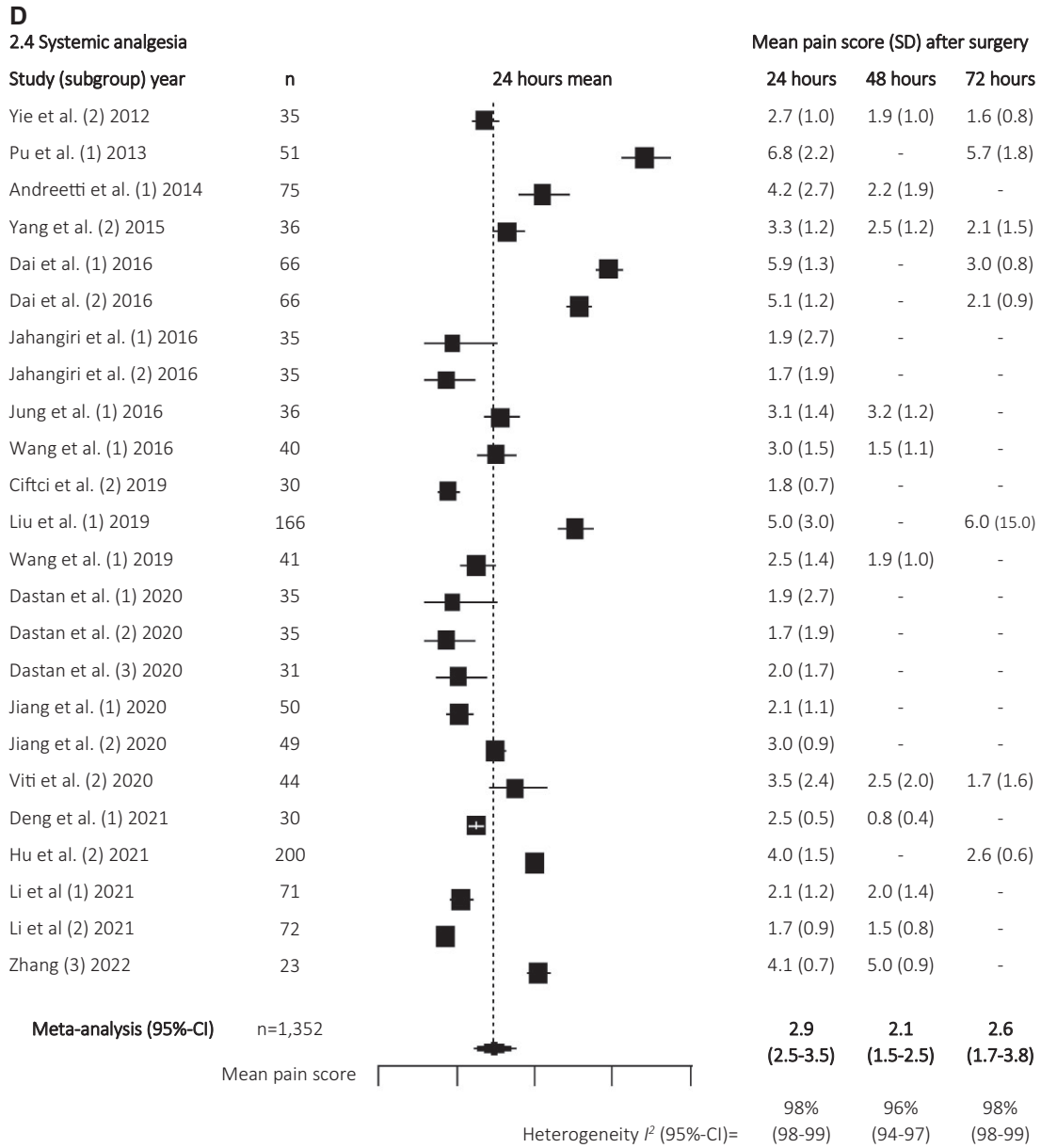


Figure 2: (Continued)

Length of hospital stay

The LOS was analysed in 46 of the 103 subgroups. The mean LOS with 95% CI and heterogeneity (I^2) for TEA was 6.7 days (5.9–7.7; I^2 = 89%), 5.3 (3.3–8.4; I^2 = 98%) for continuous regional analgesia, 4.5 (3.8–5.3; I^2 = 99%) for single-shot regional analgesia and 6.6 (5.4–8.1; I^2 = 98%) for systemic analgesia (Table 2).

Incidence of PONV

PONV was analysed in 79 of the 103 subgroups. The overall incidence of PONV with 95% CI and heterogeneity (I^2) for TEA was 18% (13–25; I^2 = 62%), 10% (5–18; I^2 = 63%) for continuous regional analgesia, 10% (7–15; I^2 = 55%) for single-shot regional analgesia and 18% (11–30; I^2 = 86%) for systemic analgesia (Table 2).

(Additional) opioids

The use of (additional) opioids was analysed in 33 of the 103 subgroups. Mean (additional) opioid use in the first 24 h after surgery was 41.0 mg (95% CI 24.9–67.4; I^2 100%) for TEA, 30.0 mg (95% CI 30.0–30.0; I^2 0%) for continuous regional analgesia, 39.2 mg (95% CI 28.0–55.0; I^2 99%) for single-shot regional analgesia and 72.7 mg (95% CI 48.0–110.1; I^2 99%) for systemic analgesia (Table 2).

Rescue analgesia

Rescue analgesia was analysed in 48 of the 103 subgroups. After TEA rescue analgesia (mainly flurbiprofen) was reported in 62% (95% CI 19–92%; I^2 98%) of the patients, after continuous regional analgesia (mainly flurbiprofen) in 37% (95% CI 20–56%; I^2 84%),

Table 2: Secondary outcomes and subgroup analyses

Type of analgesia	TEA	N^a; I^{2b}	Continuous regional	N^a; I^{2b}	Single-shot regional	N^a; I^{2b}	Systemic	N^a; I^{2b}
Secondary outcome								
LOS in days[c]	6.7 (5.9–7.7)	234; 89%	5.3 (3.3–8.4)	205; 98%	4.5 (3.8–5.3)	1,450; 99%	6.6 (5.4–8.1)	575; 98%
PONV[d]	18 (13–25)	390; 62%	10 (5–18)	361; 63%	10 (7–15)	1,364; 55%	18 (11–30)	731; 86%
Additional opioids in milligrams[c]	41.0 (24.9–67.4)	305; 100%	30.0 (30.0–30.0)	71; 0%	39.2 (28.0–55.0)	1,453; 99%	72.7 (48.0–110.1)	228; 100%
Rescue analgesia[d]	62 (19–92)	422; 98%	37 (20–56)	253; 84%	16 (10–23)	1,303; 84%	0 (0–96)	460; 0%
Subgroup analysis								
VATS technique multi-port[c]	N/A	N/A	2.3 (1.8–2.8)	362; 92%	2.3 (2.0–2.6)	2,007; 97%	2.9 (2.4–3.5)	1,293; 99%
VATS technique single-port[c]	N/A	N/A	1.5 (1.2–2.1)	161; 94%	2.4 (2.0–2.8)	278; 82%	3.5 (2.7–4.6)	503; 99%
Randomized controlled trials[c]	2.6 (1.9–3.4)	25; N/A	2.0 (1.5–2.7)	292; 90%	2.4 (1.9–3.1)	1,156; 97%	2.3 (1.9–2.8)	517; 96%
Non-randomized controlled trials[c]	1.84 (1.4–2.4)	504; 81%	1.8 (0.6–5.9)	166; 96%	2.4 (2.1–2.9)	950; 86%	4.2 (3.2–5.5)	736; 98%

[a]Sample size.
[b]Heterogeneity.
[c]Mean and 95% confidence interval.
[d]Incidence in percentage and 95% confidence interval.
LOS: length of hospital stay; PONV: postoperative nausea and vomiting; TEA: thoracic epidural analgesia; VATS: video-assisted thoracoscopic surgery; N/A: not applicable

after single-shot regional analgesia (flurbiprofen, tramadol, fentanyl) in 16% (95% CI 10–23%; I^2 84%) and after systemic analgesia (mainly NSAIDs) in 0% (95% CI 0–96%; I^2 0%) (Table 2).

Subgroup analyses based on single or multi-port thoracoscopy

All patients receiving TEA underwent multi-port VATS. In the continuous regional group, mean pain scores at 24 h with 95% CI and heterogeneity (I^2) were 2.3 (1.8–2.8; I^2 92%) after multi-port versus 1.5 (1.2–2.05; I^2 94%) after single-port thoracoscopy. In the single-shot regional group, this was 2.3 (2.0–2.6; I^2 97%) after multi-port patients versus 2.4 (2.0–2.8; I^2 82%) after single-port thoracoscopy. In the systemic analgesia group, this was 2.9 (2.4–3.5; I^2 99%) after multi-port versus 3.5 (2.7–4.6; I^2 99%) in the single-port thoracoscopy subgroups (Table 2).

Subgroup analysis based on study design

Randomized controlled trials (RCTs) versus non-RCTs reported the following mean pain scores at 24 h with 95% CI and heterogeneity (I^2): in the TEA group 2.6 (1.9–3.4; I^2 0%) versus 1.8 (1.4–2.4; I^2 81%), in the continuous analgesia group 2.0 (1.5–2.7; I^2 90%) versus 1.8 (0.6–5.9; I^2 96%), in the single-shot regional group 2.4 (1.9–3.1; I^2 97%) versus 2.4 (2.1–2.9; I^2 86%) and in the systemic analgesia group, this was 2.3 (1.9–2.8; I^2 96%) versus 4.2 (3.2–5.5; I^2 98%) (Table 2).

DISCUSSION

Looking carefully at our research question and aim, one may easily conclude that unilateral loco-regional techniques have comparable pain scores as TEA, but a shorter length of stay and lower incidence of PONV. However, despite the fact that our primary and secondary outcomes have been calculated by a random-effects meta-analysis and hence can guide us to credible conclusions, the pooled results show such a high level of variability and heterogeneity between the studies, that no firm conclusions can be drawn. Even with the careful selection of studies based on strict eligibility criteria, heterogeneity is a main concern. Possible confounding factors were statistically explored through sensitivity analysis, such as study designs (RCT vs non-RCT) and the approach of the thoracoscopy procedure (multi-port vs single port). Additionally, we describe possible confounding factors including local practices of analgesic protocols, implementation of ERATS, methodological limitations such as small sample sizes and the lack of relevant RCTs. Due to these factors, a meta-analysis and comparisons between different analgesics were untrustworthy.

This exploratory meta-analysis comprising 5573 patients undergoing thoracoscopic anatomical lung resection showed that 24 h after surgery, pooled mean pain scores and 95% CI in all analgesic groups were below the clinical threshold of a NRS pain score of 4. When performing subgroup analysis, however, non-RCTs in the continuous and systemic analgesia groups demonstrated upper boundaries of the 95% CI of 5.92 and 5.47, respectively, slightly crossing the clinical threshold of acceptable pain. Recent PROSPECT guidelines advocate using loco-regional analgesic techniques and actually discourage the use of TEA due to its association with hypotension and epidural haematomas, despite lower pain scores among patients receiving TEA in randomized studies [8]. The authors based their advice on a Delphi consensus without clear scientific evidence. In contrast with our systematic review, the PROSPECT guideline included patients with a majority not undergoing anatomical lung resection. Moreover, they did not attempt to perform a pooled meta-analysis.

Although TEA is the historic standard of care for pain management in lung surgery and has been used for decades, only 8 studies on TEA fulfilled the inclusion criteria of our systematic review, including 1 RCT [23]. In this RCT, continuous PVB had even better pain relief than TEA after 24, 36 and 48 h. One of the possible explanations addressed by the authors was that the drug distribution in TEA led to a more predictable block spread than PVB, as a result of which in the PVB, more interventions were needed to achieve sufficient block spread which may therefore have led to better pain relief. A second non-randomized study [70] used

propensity-matched analysis to compare a cohort with TEA versus single-shot intercostal nerve block (ICNB). Also in this study, ICNB as unilateral regional technique led to significantly improved average pain scores when compared to TEA. One of the possible explanations may be that all patients in the ICNB group received continuous intravenous fentanyl infusion. These figures were confirmed by a comparative cohort study by Bousema *et al.* [53], comparing TEA versus continuous ICNB, also demonstrating similar pain scores but with a higher additional use of opioids intravenously in the continuous ICNB group. It therefore appears that unilateral regional techniques, when compared to TEA, may indeed have equivalent pain reduction, but only with adjacent opioids or non-opioid analgesics as part of a multimodal analgesia strategy. The higher amount of opioid use in the systemic analgesia group strengthens the theory of regional analgesic techniques being opioid sparing [81]. Multi-modal analgesic strategies implement a variety of analgesic methods combining systemic analgesia with loco-regional anaesthetics, which result in synergistic effects to help develop more effective strategies towards ERATS while minimizing side effects [2, 82].

Our meta-analysis furthermore suggests a shorter LOS after continuous and single-shot unilateral regional analgesia compared to TEA and systemic analgesia. Next to the analgesic strategy, predefined centre-specific discharge criteria in either fast-track or non-fast-track protocols are strong predictors of LOS. In several studies solely focusing on TEA as analgesic technique, we found that the predefined protocol negatively influenced LOS in advance. In the study by Nomori *et al.* [52], all patients underwent 6-min walking and pulmonary function tests during their hospital stay at POD 7, precluding earlier discharge. Similarly, Darr *et al.* [40] explicitly described not using a fast-track protocol: TEA duration was more than 3 days and 2 chest tubes were placed. Studies directly comparing TEA versus unilateral regional analgesia could not demonstrate differences in LOS. Yamazaki *et al.* [70] evaluated TEA versus single-shot ICNB with similar LOS (7.7 vs 6.6 days). Bousema *et al.* [53] showed the same LOS for patients undergoing TEA versus continuous ICNB (median of 4 days). To the contrary, studies solely focusing on unilateral regional techniques generally used multimodal analgesic regimes [56, 68, 71] combined with predefined fast-track protocols. Single-shot techniques, although having a time-limited analgesic effect, are easy to perform and cost-effective [83]. Most studies applying single-shot techniques included only ASA I and II patients [38, 54, 55, 65] and uniportal VATS techniques [48, 71] possibly creating a selection bias of patients with an advantage in rapid recovery and early discharge. Moreover, single-shot unilateral techniques were also accompanied by adjuvants such as dexmedetomidine, nalbuphine and dexamethasone [55, 65, 78] as well as experimental studies using liposomal bupivacaine [67, 68], thereby extending the efficacy of single-shot blocks promoting ERATS. All factors taken into consideration, not only the applied analgesic technique has an impact on LOS, but the tendency to follow ERATS protocols and studies focusing on pain control, create a clear advantage resulting in early hospital discharge. Unfortunately, we could not make clear conclusions whether included studies adhered to ERATS protocols since there is no clear definition of ERATS in the included articles and therefore a separate analysis on this topic was not possible.

PONV is an important patient-centred outcome that frequently complicates the recovery after surgery. In our systematic review, it was the most frequently reported analgesic block related adverse event, other complications such as haematomas and infections did not occur. Patients with reduced PONV reported greater patient satisfaction [57]. According to recent guidelines [84], besides volatile analgesia and patient characteristics, the type of postoperative analgesic technique used is a factor that greatly influences the incidence of PONV. In this meta-analysis, as compared to other outcomes, PONV showed surprisingly lower heterogeneity for pooled percentages, indicating a certain degree of consensus. TEA and systemic analgesia show a higher incidence (18% respectively) when compared to unilateral loco-regional techniques as continuous or single-shot analgesia (10%, respectively). PONV incidence depends on the fentanyl dosage in the epidural solution. A large patient series receiving TEA with a low dosage of fentanyl have reported only 1.8% of PONV [85]. Adding regional analgesic blocks compared to patients with only general anaesthesia have 9 times less PONV [86]. Moreover, central neuraxial blocks achieved with TEA are associated with sympathetic nervous system blockade which contributes to postural hypotension induced nausea and vomiting [86]. RCTs directly comparing unilateral loco-regional techniques versus control groups without peripheral blocks demonstrate that PONV was significantly more prevalent in the control group [24, 36, 38, 57]. Finally, most studies in the unilateral loco-regional technique groups provided prophylactic anti-emetic medication, also significantly reducing PONV incidence [14, 24, 57, 64, 72, 80].

Subgroup analyses based on pain scores in multi- and single-port VATS do not show a strong relationship between number of surgical incisions and degree of pain. This statement has been thoroughly investigated and while some articles confirm a beneficial effect of single-port VATS in terms of postoperative pain, blood loss and LOS, others have confirmed similar effects or even superiority of multi-port VATS [87]. In our meta-analysis, we did not see relevant differences in pain scores regarding this controversial topic. With respect to our subgroup analysis of RCTs versus non-RCTs, TEA and continuous regional analgesia showed slightly higher pain scores in the RCTs, single-shot regional analgesia showed the same pain scores for both groups and systemic analgesia reported higher pain scores in non-RCTs. Well-performed RCTs [35, 37, 59–61, 65, 72, 80] with standardized well-reported outcomes showed lower pain scores. The GRADE system offered additional understanding on the quality of evidence of the different outcome measures resulting from this systematic review and meta-analysis. The meta-analysis for pain scores originating from the regional single-shot and the systemic analgesia groups contain numerous randomized clinical trials, which might offer a true effect that lies close to that of the estimate of the effect. The same accounts for large sample sizes with narrow CIs in outcomes such as PONV and postoperative complications, contributing to a lower heterogeneity for the studies in the meta-analysis. Outcomes throughout the different analgesic groups vary in the quality of the evidence; the use of additional opioids being the outcome that scored the lowest quality of evidence across all different analgesic techniques, making conclusions regarding this outcome challenging.

This is the first attempt to explore all written literature about analgesic technique after thoracoscopic anatomical lung resection. Beforehand, we did not anticipate such a significant heterogeneity between studies precluding valid pooling of the analgesic techniques using an analytic meta-analysis. Nevertheless, we present the meta-analysis in this paper, aiming to explore the possible causes. The forced exploratory nature of our meta-analysis is the most important limitation to be addressed, not allowing

definite conclusions on which analgesic approach is to be recommended. Small sample sizes, local analgesic protocols, implementation of ERATS, cultural differences in assessing pain, study designs and the subjective nature of pain may all have played an important role leading to high inter-study variability. Subgroup analysis of objective factors such as single or multi-port VATS and randomized or non-randomized trials did not lower the heterogeneity. Moreover, only analysing means or medians without transformation from medians to means did also not lower the heterogeneity (Supplementary Material, Appendix I). Other possible factors influencing outcomes are the number of chest tubes [88] but these were not described in most studies, as well as possible era bias, although almost all (except 1) included studies were published after 2012. Another limitation is that we only selected studies that reported pain scores, possibly limiting the external applicability regarding secondary outcomes. The included studies mainly used mean pain scores as primary outcome, whereas evidence suggests that reporting pain scores into a small number of categories provides greater clinical significance [89]. Whether pain scores are to be reported as means, medians or categorical variables remain a topic of discussion [90]. We believe an alternative outcome such as looking at the proportion of moments of pain (NRS $\geq$ 4) indicates a more clinically significant outcome when reporting pain.

CONCLUSION

Although this systematic review on optimal pain management after thoracoscopic anatomical lung resection reveals that most recent guidelines tend to advocate less invasive unilateral regional techniques for analgesia, our attempt to pool results for an analytic meta-analysis demonstrates the complexity and variability in the published literature. Systematically evaluating the available evidence, we cannot discourage nor encourage the use of TEA. In order to provide more rigorous clinical evidence, a well-designed large, randomized trial comparing continuous or single-shot unilateral regional analgesia techniques to TEA is indispensable.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENTS

We thank Bart de Vries for his help with the systematic literature research and Marta Regis and Jeanne Dieleman for their advice on statistics and methodology on how to perform and analyse the risk of bias in systematic reviews and meta-analysis. Furthermore, we kindly thank Judith ter Schure for her advice as systematic review and meta-analysis expert.

Funding

This systematic review and meta-analysis is part of the OPtriAL project funded by ZonMw (project number 10140021910007). This project aims to improve postoperative pain management after lung surgery. The funding and involved (academic) institutions have no involvement in the study design, data-analysis and interpretation of the results. Publication of the article has no conflicts of interest.

Conflict of interest: Louisa N. Spaans and Frank J.C. van den Broek report a funding grant from ZonMw during the elaboration of this study. The remaining authors declare no conflict of interest.

Data availability

Data underlying this article are available in the article and in the Supplementary Material.

Author contributions

Louisa N. Spaans: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Writing—original draft; Writing—review & editing. **Jelle E. Bousema:** Conceptualization; Data curation; Formal analysis; Writing—review & editing. **Patrick Meijer:** Conceptualization; Writing—review & editing. **R.A. (Arthur) Bouwman:** Supervision; Validation; Writing—review & editing. **Renee van den Broek:** Supervision; Validation; Writing—review & editing. **Jo Mourisse:** Conceptualization; Supervision; Validation; Writing—review & editing. **Marcel G.W. Dijkgraaf:** Conceptualization; Data curation; Methodology; Supervision; Validation; Writing—review & editing. **Ad F.T.M. Verhagen:** Supervision; Writing—review & editing. **Frank J.C. van den Broek:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing—original draft; Writing—review & editing.

Reviewer information

Interdisciplinary CardioVascular and Thoracic Surgery thanks Clemens Aigner, Lucio Cagini and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology 2006;104:594–600.
[2] Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M *et al.* Guidelines for enhanced recovery after lung surgery: recommendations of the enhanced recovery after surgery (ERAS(R)) society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg 2019;55:91–115.
[3] Sun K, Liu D, Chen J, Yu S, Bai Y, Chen C *et al.* Moderate-severe postoperative pain in patients undergoing video-assisted thoracoscopic surgery: a retrospective study. Sci Rep 2020;10:795–8.
[4] Homma T, Doki Y, Yamamoto Y, Ojima T, Shimada Y, Kitamura N *et al.* Risk factors of neuropathic pain after thoracic surgery. J Thorac Dis 2018;10:2898–907.
[5] Umari M, Carpanese V, Moro V, Baldo G, Addesa S, Lena E *et al.* Postoperative analgesia after pulmonary resection with a focus on video-assisted thoracoscopic surgery. Eur J Cardiothorac Surg 2018;53:932–8.
[6] Yoshioka M, Mori T, Kobayashi H, Iwatani K, Yoshimoto K, Terasaki H *et al.* The efficacy of epidural analgesia after video-assisted thoracoscopic surgery: a randomized control study. Ann Thorac Cardiovasc Surg 2006;12:313–8.
[7] Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anaesth 2012;109:144–54.
[8] Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M; PROSPECT Working Group of the European Society of Regional Anaesthesia and

Pain Therapy. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2022;77:311–25.
[9] Thompson C, French DG, Costache I. Pain management within an enhanced recovery program after thoracic surgery. J Thorac Dis 2018;10: S3773–80.
[10] Spaans LN, Bousema JE, van den Broek FJC. Variation in postoperative pain management after lung surgery in the Netherlands: a survey of Dutch thoracic surgeons. Br J Anaesth 2022;128:e222–5.
[11] Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia 2013;68: 1107–13.
[12] Elmore B, Nguyen V, Blank R, Yount K, Lau C. Pain management following thoracic surgery. Thorac Surg Clin 2015;25:393–409.
[13] Kaplowitz J, Papadakos PJ. Acute pain management for video-assisted thoracoscopic surgery: an update. J Cardiothorac Vasc Anesth 2012;26: 312–21.
[14] Xu J, Yang X, Hu X, Chen X, Zhang J, Wang Y. Multilevel thoracic paravertebral block using ropivacaine with/without dexmedetomidine in video-assisted thoracoscopic surgery. J Cardiothorac Vasc Anesth 2018; 32:318–24.
[15] Scimia P, Basso Ricci E, Droghetti A, Fusco P. The ultrasound-guided continuous erector spinae plane block for postoperative analgesia in video-assisted thoracoscopic lobectomy. Reg Anesth Pain Med 2017;42: 537.
[16] Adhikary SD, Pruett A, Forero M, Thiruvenkatarajan V. Erector spinae plane block as an alternative to epidural analgesia for post-operative analgesia following video-assisted thoracoscopic surgery: a case study and a literature review on the spread of local anaesthetic in the erector spinae plane. Indian J Anaesth 2018;62:75–8.
[17] Bingham AE, Fu R, Horn JL, Abrahams MS. Continuous peripheral nerve block compared with single-injection peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. Reg Anesth Pain Med 2012;37:583–94.
[18] Yeap YL, Wolfe JW, Backfish-White KM, Young JV, Stewart J, Ceppa DP *et al.* Randomized prospective study evaluating single-injection paravertebral block, paravertebral catheter, and thoracic epidural catheter for postoperative regional analgesia after video-assisted thoracoscopic surgery. J Cardiothorac Vasc Anesth 2020;34:1870–6.
[19] Anello C, Fleiss JL. Exploratory or analytic meta-analysis: should we distinguish between them? J Clin Epidemiol 1995;48:109–8.
[20] Steinthorsdottir KJ, Wildgaard L, Hansen HJ, Petersen RH, Wildgaard K. Regional analgesia for video-assisted thoracic surgery: a systematic review. Eur J Cardiothorac Surg 2014;45:959–66.
[21] De Cassai A, Boscolo A, Zarantonello F, Piasentini E, Di Gregorio G, Munari M *et al.* Serratus anterior plane block for video-assisted thoracoscopic surgery: a meta-analysis of randomised controlled trials. Eur J Anaesthesiol 2021;38:106–14.
[22] Elsayed HH, Moharram AA. Tailored anaesthesia for thoracoscopic surgery promoting enhanced recovery: the state of the art. Anaesth Crit Care Pain Med 2021;40:100846.
[23] Kosinski S, Fryzlewicz E, Wilkojc M, Cmiel A, Zielinski M. 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;48:280–7.
[24] Deng W, Liu F, Jiang CW, Sun Y, Shi GP, Zhou QH. Continuous rhomboid intercostal block for thoracoscopic postoperative analgesia. Ann Thorac Surg 2022;114:319–26.
[25] Yu H, Tian W, Xu Z, Jiang R, Jin L, Mao W *et al.* Patient-controlled intravenous analgesia with opioids after thoracoscopic lung surgery: a randomized clinical trial. BMC Anesthesiol 2022;22:253–4.
[26] Dastan F, Langari ZM, Salamzadeh J, Khalili A, Aqajani S, Jahangirifard A. A comparative study of the analgesic effects of intravenous ketorolac, paracetamol, and morphine in patients undergoing video-assisted thoracoscopic surgery: a double-blind, active-controlled, randomized clinical trial. Ann Card Anaesth 2020;23:177–82.
[27] McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. Biom J 2020;62:69–98.
[28] McGrath S, Zhao X, Qin ZZ, Steele R, Benedetti A. One-sample aggregate data meta-analysis of medians. Stat Med 2019;38:969–84.
[29] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res . 2018 Jun;27(6):1785–1805.
[30] Wan X, Wang W, Liu Jiming, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014, 14:135.
[31] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[32] Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
[33] Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[34] Olsen MF, Bjerre E, Hansen MD, Hilden J, Landler NE, Tendal B *et al.* Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med 2017;15:35.
[35] 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 2019;45:10–15.
[36] Ciftci B, Ekinci M, Celik EC, Tukac IC, Bayrak Y, Atalay YO. Efficacy of an ultrasound-guided erector spinae plane block for postoperative analgesia management after video-assisted thoracic surgery: a prospective randomized study. J Cardiothorac Vasc Anesth 2020;34:444–9.
[37] Liu Z, Yang R, Shao F. Comparison of postoperative pain and recovery between single-port and two-port thoracoscopic lobectomy for lung cancer. Thorac Cardiovasc Surg 2019;67:142–6.
[38] Park MH, Kim JA, Ahn HJ, Yang MK, Son HJ, Seong BG. A randomised trial of serratus anterior plane block for analgesia after thoracoscopic surgery. Anaesthesia 2018;73:1260–4.
[39] Kadomatsu Y, Mori S, Ueno H, Uchiyama M, Wakai K. 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;66:425–31.
[40] Darr C, Cheufou D, Weinreich G, Hachenberg T, Aigner C, Kampe S. Robotic thoracic surgery results in shorter hospital stay and lower postoperative pain compared to open thoracotomy: a matched pairs analysis. Surg Endosc 2017;31:4126–30.
[41] Dai F, Meng S, Mei L, Guan C, Ma Z. Single-port video-assisted thoracic surgery in the treatment of non-small cell lung cancer: a propensity-matched comparative analysis. J Thorac Dis 2016;8:2872–8.
[42] Jahangiri Fard A, Farzanegan B, Khalili A, Ebrahimi Ahmadabad N, Daneshvar Kakhaki A, Parsa T *et al.* Paracetamol instead of ketorolac in post-video-assisted thoracic surgery pain management: a randomized trial. Anesth Pain Med 2016;6:e39175.
[43] Wang X, Wang K, Wang B, Jiang T, Xu Z, Wang F *et al.* Effect of oxycodone combined with dexmedetomidine for intravenous patient-controlled analgesia after video-assisted thoracoscopic lobectomy. J Cardiothorac Vasc Anesth 2016;30:1015–21.
[44] Jung J, Park SY, Haam S. Efficacy of subpleural continuous infusion of local anesthetics after thoracoscopic pulmonary resection for primary lung cancer compared to intravenous patient-controlled analgesia. J Thorac Dis 2016;8:1814–9.
[45] Yang HC, Lee JY, Ahn S, Cho S, Kim K, Jheon S *et al.* Pain control of thoracoscopic major pulmonary resection: is pre-emptive local bupivacaine injection able to replace the intravenous patient controlled analgesia? J Thorac Dis 2015;7:1960–9.
[46] Andreetti C, Menna C, Ibrahim M, Ciccone AM, D'Andrilli A, Venuta F *et al.* Postoperative pain control: videothoracoscopic versus conservative mini-thoracotomic approach. Eur J Cardiothorac Surg 2014;46:907–12.
[47] Yie JC, Yang JT, Wu CY, Sun WZ, Cheng YJ. Patient-controlled analgesia (PCA) following video-assisted thoracoscopic lobectomy: comparison of epidural PCA and intravenous PCA. Acta Anaesthesiol Taiwan 2012;50: 92–5.
[48] Hsieh MJ, Wang KC, Liu HP, Gonzalez-Rivas D, Wu CY, Liu YH *et al.* Management of acute postoperative pain with continuous intercostal nerve block after single port video-assisted thoracoscopic anatomic resection. J Thorac Dis 2016;8:3563–71.
[49] Nomori H, Cong Y, Sugimura H. Limited thoracotomy for segmentectomy: a comparison of postoperative pain with thoracoscopic lobectomy. Surg Today 2016;46:1243–8.
[50] Pu Q, Ma L, Mei J, Zhu Y, Che G, Lin Y *et al.* Video-assisted thoracoscopic surgery versus posterolateral thoracotomy lobectomy: a more patient-friendly approach on postoperative pain, pulmonary function and shoulder function. Thorac Cancer 2013;4:84–9.

[51] Wildgaard K, Petersen RH, Hansen HJ, Moller-Sorensen H, Ringsted TK, Kehlet H. Multimodal analgesic treatment in video-assisted thoracic surgery lobectomy using an intraoperative intercostal catheter. Eur J Cardiothorac Surg 2012;41:1072–7.
[52] Nomori H, Horio H, Naruke T, Suemasu K. What is the advantage of a thoracoscopic lobectomy over a limited thoracotomy procedure for lung cancer surgery? Ann Thorac Surg 2001;72:879–84.
[53] Bousema JE, Dias EM, Hagen SM, Govaert B, Meijer P, van den Broek FJC. Subpleural multilevel intercostal continuous analgesia after thoracoscopic pulmonary resection: a pilot study. J Cardiothorac Surg 2019;14: 179.
[54] Wang L, Wang Y, Zhang X, Zhu X, Wang G. Serratus anterior plane block or thoracic paravertebral block for postoperative pain treatment after uniportal video-assisted thoracoscopic surgery: a retrospective propensity-matched study. J Pain Res 2019;12:2231–8.
[55] Gao Z, Xiao Y, Wang Q, Li Y. Comparison of dexmedetomidine and dexamethasone as adjuvant for ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: a randomized, double-blind, placebo-controlled trial. Ann Transl Med 2019;7:668.
[56] 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.
[57] Yao Y, Fu S, Dai S, Yun J, Zeng M, Li H *et al.* Impact of ultrasound-guided erector spinae plane block on postoperative quality of recovery in video-assisted thoracic surgery: a prospective, randomized, controlled trial. J Clin Anesth 2020;63:109783.
[58] Jiang H, Zheng Y, Liu C, Bao Y. Postoperative analgesia effects of sulfentanyl plus dexmedetomidine in patients received VAT. Pteridines 2020; 31:55–60.
[59] Viti A, Bertoglio P, Zamperini M, Tubaro A, Menestrina N, Bonadiman S *et al.* Serratus plane block for video-assisted thoracoscopic surgery major lung resection: a randomized controlled trial. Interact CardioVasc Thorac Surg 2020;30:366–72.
[60] Lee J, Lee DH, Kim S. Serratus anterior plane block versus intercostal nerve block for postoperative analgesic effect after video-assisted thoracoscopic lobectomy: a randomized prospective study. Medicine (Baltimore) 2020;99:e22102.
[61] Kang K, Meng X, Li B, Yuan J, Tian E, Zhang J *et al.* Effect of thoracic paravertebral nerve block on the early postoperative rehabilitation in patients undergoing thoracoscopic radical lung cancer surgery. World J Surg Oncol 2020;18:298.
[62] Hu CG, Zheng K, Liu GH, Li ZL, Zhao YL, Lian JH *et al.* Effectiveness and postoperative pain level of single-port versus two-port thoracoscopic lobectomy for lung cancer: a retrospective cohort study. Gen Thorac Cardiovasc Surg 2021;69:318–25.
[63] Baldinelli F, Capozzoli G, Pedrazzoli R, Feil B, Pipitone M, Zaraca F. Are thoracic wall blocks efficient after video-assisted thoracoscopy surgery-lobectomy pain? A comparison between serratus anterior plane block and intercostal nerve block. J Cardiothorac Vasc Anesth 2021;35: 2297–302.
[64] Qiu L, Bu X, Shen J, Li M, Yang L, Xu Q *et al.* Observation of the analgesic effect of superficial or deep anterior serratus plane block on patients undergoing thoracoscopic lobectomy. Medicine (Baltimore) 2021;100: e24352.
[65] Rao J, Gao Z, Qiu G, Gao P, Wang Q, Zhong W *et al.* Nalbuphine and dexmedetomidine as adjuvants to ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: a randomized, double-blind, placebo-controlled trial. Medicine (Baltimore) 2021;100:e26962.
[66] Li Q, Yao H, Xu M, Wu J. Dexmedetomidine combined with sufentanil and dezocine-based patient-controlled intravenous analgesia increases female patients' global satisfaction degree after thoracoscopic surgery. J Cardiothorac Surg 2021;16:102–4.
[67] Weksler B, Sullivan JL, Schumacher LY. Randomized trial of bupivacaine with epinephrine versus bupivacaine liposome suspension in patients undergoing minimally invasive lung resection. J Thorac Cardiovasc Surg 2021;161:1652–61.
[68] Marciniak DA, Alfirevic A, Hijazi RM, Ramos DJ, Duncan AE, Gillinov AM *et al.* Intercostal blocks with liposomal bupivacaine in thoracic surgery: a retrospective cohort study. J Cardiothorac Vasc Anesth 2021;35:1404–9.
[69] Miyoshi H, Nakamura R, Kido H, Narasaki S, Watanabe T, Yokota M *et al.* Impact of fentanyl on acute and chronic pain and its side effects when used with epidural analgesia after thoracic surgery in multimodal analgesia: a retrospective cohort study. Ann Palliat Med 2021;10: 5119–27.
[70] Yamazaki S, Koike S, Eguchi T, Matsuoka S, Takeda T, Miura K *et al.* Preemptive intercostal nerve block as an alternative to epidural analgesia. Ann Thorac Surg 2022;114:257–64.
[71] Tan JW, Mohamed JS, Tam JKC. Incorporation of an intercostal catheter into a multimodal analgesic strategy for uniportal video-assisted thoracoscopic surgery: a feasibility study. J Cardiothorac Surg 2021;16:210.
[72] Qiu Y, Wu J, Huang Q, Lu Y, Xu M, Mascha EJ *et al.* Acute pain after serratus anterior plane or thoracic paravertebral blocks for video-assisted thoracoscopic surgery: a noninferiority randomised trial. Eur J Anaesthesiol 2021;38:S97–105.
[73] Chen JQ, Chen JR, Wang S, Gao W, Gu H, Yang XL *et al.* Effect of perineural dexamethasone with ropivacaine in continuous serratus anterior plane block for postoperative analgesia in patients undergoing video-assisted thoracoscopic surgery. J Pain Res 2022;15:2315–25.
[74] Yang J, Zhao M, Zhang XR, Wang XR, Wang ZH, Feng XY *et al.* Ropivacaine with dexmedetomidine or dexamethasone in a thoracic paravertebral nerve block combined with an erector spinae plane block for thoracoscopic lobectomy analgesia: a randomized controlled trial. Drug Des Devel Ther 2022;16:1561–71.
[75] Banks K, Ely S, Hsu DS, Dominguez DA, Gologorsky RC, Wei J *et al.* Intercostal nerve blockade with liposomal bupivacaine reduces length of stay after video assisted thoracic surgery (VATS) lobectomy. J Thorac Dis 2022;14:18–25.
[76] Zhang JW, Feng XY, Yang J, Wang ZH, Wang Z, Bai LP. Ultrasound-guided single thoracic paravertebral nerve block and erector spinae plane block for perioperative analgesia in thoracoscopic pulmonary lobectomy: a randomized controlled trial. Insights Imaging 2022;13:16–x.
[77] Turhan Ö, Sivrikoz N, Sungur Z, Duman S, Özkan B, Şentürk M. 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;35:2920–7.
[78] Er J, Xia J, Gao R, Yu Y. A randomized clinical trial: optimal strategies of paravertebral nerve block combined with general anesthesia for postoperative analgesia in patients undergoing lobectomy: a comparison of the effects of different approaches for serratus anterior plane block. Ann Palliat Med 2021;10:11464–72.
[79] Bai Y, Sun K, Xing X, Zhang F, Sun N, Gao Y *et al.* Postoperative analgesic effect of hydromorphone in patients undergoing single-port video-assisted thoracoscopic surgery: a randomized controlled trial. J Pain Res 2019;12:1091–101.
[80] Taketa Y, Irisawa Y, Fujitani T. Programmed intermittent bolus infusion versus continuous infusion of 0.2% levobupivacaine after ultrasound-guided thoracic paravertebral block for video-assisted thoracoscopic surgery: a randomised controlled trial. Eur J Anaesthesiol 2019;36:272–8.
[81] Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg 2017;125:1749–60.
[82] Crumley S, Schraag S. The role of local anaesthetic techniques in ERAS protocols for thoracic surgery. J Thorac Dis 2018;10:1998–2004.
[83] Wurnig PN, Lackner H, Teiner C, Hollaus PH, Pospisil M, Fohsl-Grande B *et al.* Is intercostal block for pain management in thoracic surgery more successful than epidural anaesthesia? Eur J Cardiothorac Surg 2002;21: 1115–9.
[84] Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS *et al.* Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2020;131:411–48.
[85] Manassero A, Bossolasco M, Carrega M, Coletta G. Postoperative thoracic epidural analgesia: adverse events from a single-center series of 3126 patients. Local Reg Anesth 2020;13:111–9.
[86] Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: a simple yet complex problem. Anesth Essays Res 2016; 10:388–96.
[87] Yan Y, Huang Q, Han H, Zhang Y, Chen H. Uniportal versus multiportal video-assisted thoracoscopic anatomical resection for NSCLC: a meta-analysis. J Cardiothorac Surg 2020;15:238–2.
[88] Huang L, Kehlet H, Holbek BL, Jensen TK, Petersen RH. Efficacy and safety of omitting chest drains after video-assisted thoracoscopic surgery: a systematic review and meta-analysis. J Thorac Dis 2021;13: 1130–42.
[89] Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y. The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology 2001;95:1356–61.
[90] Kim TK. Practical statistics in pain research. Korean J Pain 2017;30:243–9.