Review Article

Prognostic factors for chronic post-surgical pain after lung and pleural surgery: a systematic review with meta-analysis, meta-regression and trial sequential analysis

P. R. D. Clephas,[1] **S. E. Hoeks,**[2] **P. M. Singh,**[3] **C. S. Guay,**[4,5] **M. Trivella,**[6] **M. Klimek**[7] and **M. Heesen**[8]

1 PhD student, Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands
2 Associate Professor and Epidemiologist, 7 Director Residency Training and Vice-Chairman, Department of Anaesthesia, Erasmus University Medical Center, Rotterdam, The Netherlands
3 Assistant Professor, Department of Anaesthesia, Washington University School of Medicine in St. Louis, St. Louis, MO, USA
4 Fellow, Department of Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
5 Fellow, Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA
6 Honorary Senior Statistician, Centre for Statistics in Medicine, University of Oxford, Oxford, UK
8 Consultant, Department of Anaesthesia, Kantonsspital Baden AG, Baden, Switzerland

Summary

Chronic post-surgical pain is known to be a common complication of thoracic surgery and has been associated with a lower quality of life, increased healthcare utilisation, substantial direct and indirect costs, and increased long-term use of opioids. This systematic review with meta-analysis aimed to identify and summarise the evidence of all prognostic factors for chronic post-surgical pain after lung and pleural surgery. Electronic databases were searched for retrospective and prospective observational studies as well as randomised controlled trials that included patients undergoing lung or pleural surgery and reported on prognostic factors for chronic post-surgical pain. We included 56 studies resulting in 45 identified prognostic factors, of which 16 were pooled with a meta-analysis. Prognostic factors that increased chronic post-surgical pain risk were as follows: higher postoperative pain intensity (day 1, 0–10 score), mean difference (95%CI) 1.29 (0.62–1.95), $p < 0.001$; pre-operative pain, odds ratio (95%CI) 2.86 (1.94–4.21), $p < 0.001$; and longer surgery duration (in minutes), mean difference (95%CI) 12.07 (4.99–19.16), $p < 0.001$. Prognostic factors that decreased chronic post-surgical pain risk were as follows: intercostal nerve block, odds ratio (95%CI) 0.76 (0.61–0.95) $p = 0.018$ and video-assisted thoracic surgery, 0.54 (0.43–0.66) $p < 0.001$. Trial sequential analysis was used to adjust for type 1 and type 2 errors of statistical analysis and confirmed adequate power for these prognostic factors. In contrast to other studies, we found that age had no significant effect on chronic post-surgical pain and there was not enough evidence to conclude on sex. Meta-regression did not reveal significant effects of any of the study covariates on the prognostic factors with a significant effect on chronic post-surgical pain. Expressed as grading of recommendations, assessment, development and evaluations criteria, the certainty of evidence was high for pre-operative pain and video-assisted thoracic surgery, moderate for intercostal nerve block and surgery duration and low for postoperative pain intensity. We thus identified actionable factors which can be addressed to attempt to reduce the risk of chronic post-surgical pain after lung surgery.

Correspondence to: M. Heesen
Email: michael.heesen@ksb.ch
Accepted: 13 March 2023
Keywords: chronic pain; meta-analysis; prognosis; pulmonary surgical procedures; thoracic surgery

Introduction

Lung and pleural surgery are among the most common types of thoracic surgery, and are associated with the development of chronic post-surgical pain (defined as surgery-related pain that persists for at least 3 months [1, 2]). Chronic post-surgical pain after thoracic surgery generally follows very intense acute postoperative pain and later becomes chronic, often persisting for months or even years [3]. The pain often has a neuropathic component and can present itself as referred pain in other regions of the body [4, 5].

The incidence of chronic post-surgical pain after thoracic surgery has been reported to be 57% after 3 months and 47% after 6 months, which is the highest incidence of among all types of surgery [3, 6, 7]. It is associated with a lower overall quality of life [8–12]; increased utilisation of healthcare; increased absenteeism; decreased work effectiveness; and substantial societal costs [13–16]. Lung and pleural surgery are often performed for various types of cancer, making chronic post-surgical pain especially burdensome for cancer survivors given the increased life expectancy with modern cancer treatment [17]. Furthermore, both chronic post-surgical pain and thoracic surgery often result in long-term opioid use, which contributes to overuse, misuse and addiction [18–21].

Prognostic factors can help with clinical decision-making by improving individualised risk prediction. Additionally, modifiable prognostic factors are also useful as targets for the development of preventive measures and new treatment strategies [22]. Many primary prognostic factor studies are being published each year, often with heterogenous methods and inconsistent findings, making systematic reviews and meta-analyses useful to summarise the evidence [23, 24].

Prognostic factors for chronic post-surgical pain have been assessed for thoracic surgery in general [25], video-assisted thoracic surgery in general [26] or cardiac surgery only [27, 28]. However, since thoracic surgery encompasses many heterogeneous types of surgery, mechanisms for developing chronic post-surgical pain are likely to differ among types of thoracic surgery. A systematic review and meta-analysis focusing only on prognostic factors for chronic post-surgical pain after lung or pleural surgery has not yet been performed.

This systematic review and meta-analysis therefore aimed to identify all studies that report on prognostic factors for chronic post-surgical pain after lung and pleural surgery and to summarise the evidence for each identified prognostic factor. Additionally, we aimed to use trial sequential analysis to address multiplicity due to repeated significance testing, and to determine whether enough evidence has been reached for the identified prognostic factors.

Methods

The reporting of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist [29]. We used the guide for systematic reviews and meta-analyses for prognostic factor studies from the prognosis research strategy group in the design [24] and the study methods have also been described in detail in our published protocol [30].

Studies were eligible when they reported on any prognostic factor of interest for surgery-related pain; were conducted in any healthcare setting; included any population aged 18 y or older who underwent any type of lung or pleural surgery; and had a follow-up period of at least 3 months. We included retrospective and prospective observational studies as well as randomised controlled trials, considering that interventions can also be prognostic factors. Conference papers, case reports, case series and literature studies were excluded as they have few or no primary data. We aimed to assess the following prognostic factors: pre-operative pain; postoperative pain; pain catastrophising score; age; sex; BMI; diabetes mellitus; exercise tolerance; malignant disease; chemotherapy; radiation therapy; surgery duration; anaesthesia technique and surgical technique. Other prognostic factors were considered when reported by at least three studies.

Medline, Scopus, Web of Science, Embase, Cochrane, CINAHL and Google Scholar were searched from inception until 27 June 2022. The search was supplemented with reference searches of relevant (literature) studies. The systematic search was built and adapted for each database by an experienced information scientist [31] (see online Supporting Information Appendix S1). No restrictions on language, study status or time of publication were placed. Two independent teams of reviewers (PC alone and PS and CG together) screened the articles based on the eligibility criteria in a title and abstract phase and a full-text phase. Differences were resolved through a consensus meeting or by consultation of a fourth reviewer (MH).

Data were stored in a study characteristics table and a prognostic factors table. For the study characteristics table, the following were extracted: first author; year; study type; country; study period; inclusion and exclusion criteria; number of patients completing study; chronic post-surgical

pain definition; number of chronic post-surgical pain cases; time between chronic post-surgical pain assessment and surgery; age; number of females; number of video-assisted thoracic operations; number of malignant diseases; number of regional anaesthesia; type of regional anaesthesia; and potential prognostic factors. The following were extracted for the prognostic factors table: first author; year; prognostic factor details; chronic post-surgical pain definition; number of chronic post-surgical pain cases (exposed and unexposed to the prognostic factor); estimates for each group; unadjusted effect measure; adjusted effect measure; and covariates that were adjusted for.

The same two independent teams of reviewers assessed the quality of each included study with the quality in prognostic studies tool [32]. Differences were resolved through a consensus meeting.

Odds ratios (OR), risk ratios (RR) and hazard ratios were considered as effect measures for both continuous and categorical prognostic factors, and the mean difference for the continuous prognostic factors only. Adjusted and unadjusted effect measures as well as every type of effect measure were reported separately. When the mean (SD) values were not directly reported, they were calculated from the median (IQR) [33]. When no effect measures were directly reported, the mean difference was calculated for continuous prognostic factors and the OR for categorical prognostic factors.

A meta-analysis was performed for prognostic factors reported by at least five studies when similar effect measures were reported or could be calculated [34]. In addition to the overall pooled effect measure, separate effect measures were calculated and presented for randomised trials and observational studies. We used a random effects model with the DerSimonian and Laird estimator and included the 95% prediction interval (95%PI) in addition to the 95%CI [35–37]. The Q and I^2 statistics were calculated to quantify the presence of heterogeneity [38]. For other prognostic factors, only the direction of effect of the studies was described.

Sensitivity analyses were performed by excluding studies reporting neuropathic pain or a pain threshold as chronic post-surgical pain definition. Subgroup analyses and meta-regression were used to explore possible sources of heterogeneity. Subgroup analyses were performed for neuropathic pain; video-assisted thoracic surgery (≥ 50% of patients); malignant disease (≥ 50% of patients) and regional anaesthesia (≥ 50% of patients). Univariable meta-regression was performed with follow-up time in months; sex (proportion of females); video-assisted thoracic surgery (proportion of patients); malignant disease (proportion of patients) and regional anaesthesia (% patients) for prognostic factors reported by at least 10 studies with similar effect measures [39].

Given the high number of studies and prognostic factors that were found to be significantly associated with the outcome in our conventional meta-analyses, we decided to account for the risk of spurious findings. We extended the methodology as described in our study protocol [30], and additionally added trial sequential analysis to exclude the possibility that type 1 and type 2 errors could hamper the confidence into our results. Trial sequential analysis was therefore performed for prognostic factors summarised with a meta-analysis to account for type 1 and type 2 errors and to determine whether enough evidence had been reached. The required information size, defined as the sample size needed to detect or reject an a priori assumed effect in meta-analyses, was calculated with a type 1 error of 0.05, type 2 error of 0.20 and the effect measures obtained from the conventional meta-analyses. O'Brien-Fleming and futility boundaries were constructed using the O'Brien-Fleming alpha-spending function and a correction was applied for heterogeneity based on model variance. When the O'Brien-Fleming boundaries are crossed, evidence for the presence of an effect can be assumed. In contrast, crossing the futility boundaries means that lack of an effect can be assumed. We have described methods for trial sequential analysis in detail elsewhere [40, 41]. The presence of publication bias was assessed for prognostic factors reported by at least 10 studies with similar effect measures by inspecting funnel plots and statistically testing for asymmetry [42–46]. All calculations and analyses were performed with the Metafor package for R and the trial sequential analysis software of the Copenhagen Trial Unit [47, 48].

The grades of recommendation assessment, development and evaluation (GRADE) guideline [28] was used for the certainty assessment of the pooled effect measures of each prognostic factor, based on risk of bias, imprecision, inconsistency, indirectness and publication bias [49]. Since the required information size can be considered a measure of imprecision, we have refrained from certainty of evidence assessments for prognostic factors where the required information size was not reached.

Results

The systematic search identified a total of 5100 records. After removal of 3025 duplicates, 2075 were screened on title and abstract, after which 210 remained. An additional

12 records were identified through reference searching, resulting in a total of 222 for the full-text screening. After removal of 166 records, 56 that met the eligibility criteria were included (Fig. 1) [9, 11, 50–103]. Of the 56 included studies, 28 (50%) were randomised controlled trials, 16 (29%) prospective observational studies and 12 (21%) retrospective observational studies. The studies included a total of 10,038 patients of whom 4394 (44%) were female and with a total of 2943 (29%) chronic post-surgical pain cases. The patients were aged on average 60.26 y. The full study characteristics are included in online Supporting Information Table S1; a summary of the main features is included in Table 1.

The full quality assessment of the studies is included in online Supporting Information Table S2 and a summary is included in Fig. 2. We judged there to be a high risk of bias in 14 studies (25%) for study participation, 12 studies (21%) for study attrition, none for prognostic measurement, six studies (11%) for outcome measurement, 18 studies (32%) for study confounding and none for statistical analysis and reporting.

We identified a total of 45 prognostic factors for chronic post-surgical pain after lung and pleural surgery, which could be categorised into 13 anaesthesia-related prognostic factors, 20 patient-related prognostic factors and 12 surgery-related prognostic factors. The extracted data for each prognostic factor are included in online Supporting Information Tables S3–S8. A meta-analysis was performed for four anaesthesia-, eight patient- and four surgery-related prognostic factors, of which the main findings are summarised in Table 2 and in detail in online Supporting Information Tables S9–S11. For the prognostic factors not summarised with a meta-analysis, the directions of effect for each prognostic factor are summarised in Fig. 3 and in detail in online Supporting Information Tables S12–S14.

Of the anaesthesia-related prognostic factors, meta-analysis and trial sequential analysis were performed for epidural analgesia, intercostal nerve block, paravertebral analgesia and peri-operative ketamine (online Supporting Information Figs. S1–S8). Intercostal nerve block significantly lowered the risk of chronic post-surgical pain with an OR (95%CI) of 0.76 (0.61–0.95), p = 0.018 (Fig. 4), while epidural analgesia, paravertebral analgesia and peri-operative ketamine had no significant effect on chronic post-surgical pain.

Trial sequential analysis showed futility for epidural analgesia and paravertebral analgesia, since the z-curve crossed the futility boundaries (online Supporting Information Figs. S5 and S7). For peri-operative ketamine,

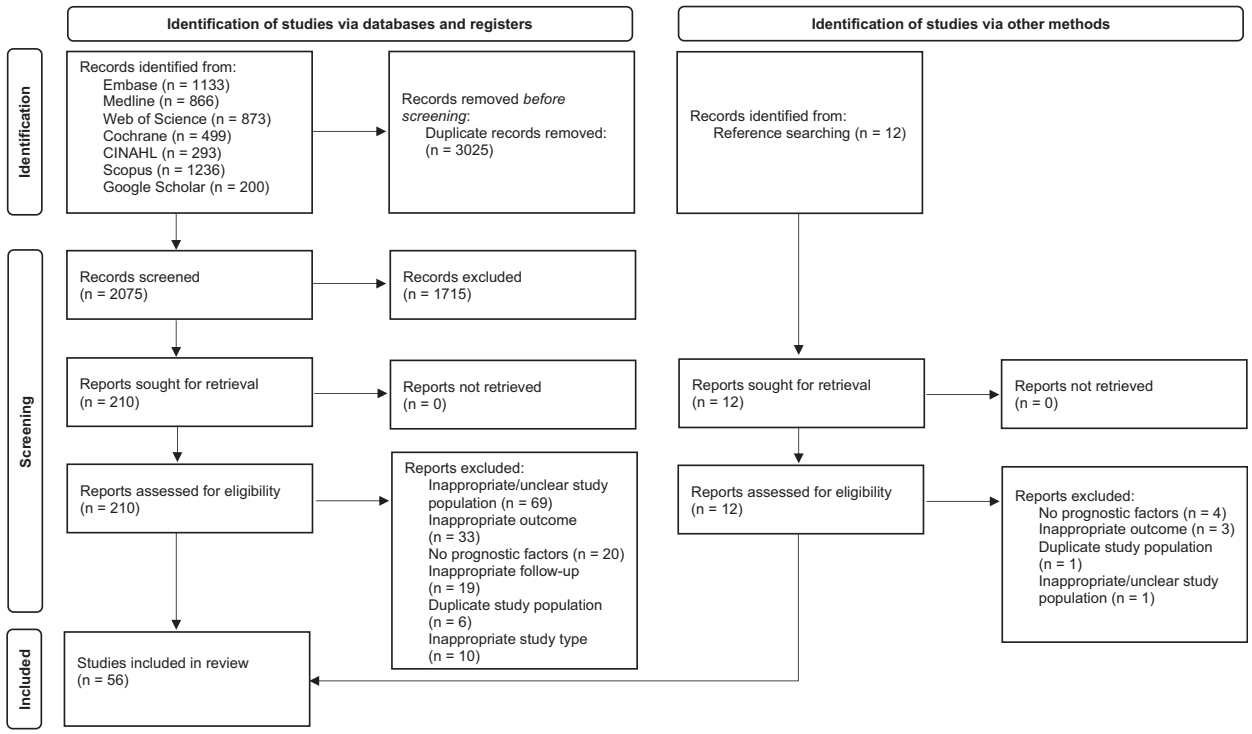

Figure 1 Study selection flowchart.

Table 1 Characteristics of the included studies. Values are number (proportion).

Geographical region	
Asia	20 (36%)
Europe	16 (29%)
USA	6 (11%)
Middle East	6 (11%)
UK	5 (9%)
Canada	3 (5%)
Study type	
Randomised controlled trial	28 (50%)
Prospective observational	16 (29%)
Retrospective observational	12 (21%)
Primary pain measurement scale	
Reporting of any pain	24 (43%)
Numerical rating scale score	20 (36%)
LANSS score	5 (9%)
NPSI score	3 (5%)
Visual analogue scale score	3 (5%)
GSNP score	1 (2%)
Time between surgery and CPSP assessment	
3–6 months	38 (68%)
6–12 months	16 (29%)
>12 months	2 (4%)

LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NPSI, Neuropathic Pain Symptom Inventory; GSNP, Grading System for Neuropathic Pain; CPSP, chronic post-surgical pain.

trial sequential analysis showed inadequate power of the meta-analysis as the O'Brien-Fleming, futility and required information size boundaries were not crossed (online Supporting Information Fig. S8). For intercostal nerve block, trial sequential analysis showed adequate power of the meta-analysis as the z-curve crossed both conventional and required information size boundaries (online Supporting Information Fig. S6).

Nine anaesthesia-related prognostic factors were summarised with the directions of effect. The studies reporting on peri-operative gabapentin were all in the direction of decreasing chronic post-surgical pain risk, the other anaesthesia-related prognostic factors were either reported by very few studies or had inconsistent directions of effect.

Of the patient-related prognostic factors, meta-analysis and trial sequential analysis were performed for age; ASA physical status (3/4 vs.1/2/IV vs. I/II); BMI; malignant disease; postoperative pain intensity (0–10 score on day 1); pre-operative pain; sex (female vs. male) and smoking (online Supporting Information Figs. S9–S24). Higher postoperative pain intensity, mean difference (95%CI) 1.29 (0.62–1.95), $p < 0.001$; pre-operative pain, OR (95%CI) 2.86 (1.94–4.21), $p < 0.001$; and female sex, OR (95%CI) 1.29 (1.04–1.60), $p = 0.019$, significantly increased the risk of chronic post-surgical pain (Figs. 5–7). The ASA physical status, BMI, malignant disease and smoking had no significant effect on chronic post-surgical pain.

Trial sequential analysis showed futility for ASA physical status (online Supporting Information Figure S18), and inadequate power of the meta-analyses for age, BMI, malignant diseases, sex and smoking (online Supporting Information Figs. S17, S19, S20, S23, S24). For postoperative pain intensity and pre-operative pain, trial sequential analysis showed adequate power of the meta-analyses (online Supporting Information Figs. S21 and S22).

In all, 12 patient-related prognostic factors were summarised with the directions of effect. The studies reporting on pre-operative anxiety score, pre-operative depression score and pre-operative pain catastrophising score were all in the direction of increasing chronic post-surgical pain risk with higher values. The other patient-related prognostic factors were either reported by very few studies or had inconsistent directions of effect.

Finally, of the surgery-related prognostic factors, meta-analysis and trial sequential analysis were performed for chest tube duration (in days), lobectomy, surgery duration (in minutes) and video-assisted thoracic surgery (vs. open thoracotomy) (online Supporting Information Figs. S25–S32). Higher surgery duration with mean difference (95%CI) 12.07 (4.99–19.16), $p < 0.001$, significantly increased the

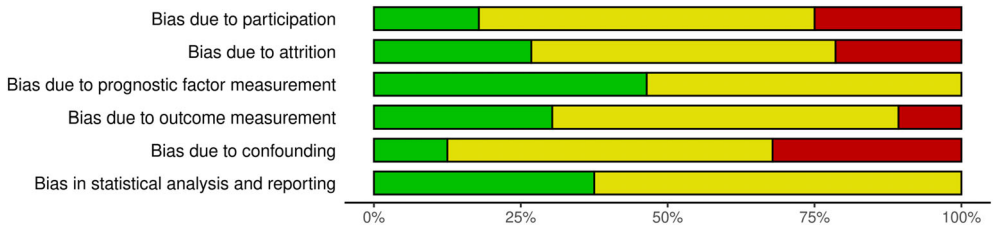

Figure 2 Quality assessment results. Green: low risk of bias; yellow: moderate risk of bias; red: high risk of bias.

Table 2 Main results of the meta-analyses.

Prognostic factor	Studies (meta-analysis)	n/RIS	Pooled effect measure (95%CI)	95%PI	I^2	p value	Quality of evidence
Epidural analgesia	12 (11)	4609/2610	1.11 (OR) (0.86–1.42)	0.72–1.70	18%	0.438	⊕⊕⊕⊖
Intercostal nerve block	5 (5)	3959/1723	0.76 (OR) (0.61–0.95)	0.61–0.95	0%	0.018	⊕⊕⊕⊖
Paravertebral analgesia	7 (7)	3696/181	1.03 (OR) (0.60–1.78)	0.43–2.49	23%	0.916	⊕⊕⊕⊕
Peri-operative ketamine	6 (6)	382/11,448	0.83 (OR) (0.45–1.54)	0.27–2.55	40%	0.550	RIS not reached
Age	20 (16)	5467/46,788	−0.91 (MD) (−2.78–0.95)	−7.09–5.26	82%	0.336	RIS not reached
ASA physical status	5 (5)	3772/1643	0.99 (OR) (0.75–1.32)	0.75–1.32	0%	0.961	⊕⊕⊕⊕
BMI	7 (6)	3969/16,556	0.14 (MD) (−0.11–0.38)	−0.11–0.38	0%	0.201	RIS not reached
Malignant disease	6 (6)	799/353,836	1.32 (OR) (0.69–2.51)	0.36–4.87	54%	0.398	RIS not reached
Postoperative pain intensity	13 (6)	524/288	1.29 (MD) (0.62–1.95)	−0.01–2.58	58%	<0.001	⊕⊕⊖⊖
Pre-operative pain	8 (6)	622/90	2.86 (OR) (1.94–4.21)	1.94–4.21	0%	<0.001	⊕⊕⊕⊕
Sex	18 (17)	6003/10,954	1.29 (OR) (1.04–1.60)	0.74–2.27	44%	0.019	RIS not reached
Smoking	6 (6)	4235/146,888	1.08 (OR) (0.76–1.53)	0.54–2.18	58%	0.666	RIS not reached
Chest tube duration	8 (5)	658/2529	0.74 (MD) (−0.27–1.76)	−1.41–2.89	82%	0.151	RIS not reached
Lobectomy	7 (7)	4586/43,775	1.07 (OR) (0.76–1.53)	0.49–2.34	64%	0.688	RIS not reached
Surgery duration	12 (9)	4185/2950	12.07 (MD) (4.99–19.16)	−3.92–28.07	55%	<0.001	⊕⊕⊕⊖
VATS	13 (13)	5904/1167	0.54 (OR) (0.43–0.66)	0.33–0.86	36%	<0.001	⊕⊕⊕⊕

RIS, required information size; PI, prediction interval; OR, odds ratio; MD, mean difference; VATS, video-assisted thoracic surgery.

risk of chronic post-surgical pain, and video-assisted thoracic surgery with an OR (95%CI) 0.54 (0.43–0.66), $p < 0.001$, significantly decreased the risk (Figs. 8 and 9). Chest tube duration and lobectomy had no significant effect on chronic post-surgical pain.

For chest tube duration and lobectomy, trial sequential analysis showed inadequate power of the meta-analyses (online Supporting Information Figs. S29 and S30), and adequate power for the meta-analyses of surgery duration and video-assisted thoracic surgery (online Supporting Information Figs. S31 and S32).

Eight surgery-related prognostic factors were summarised with the directions of effect. The studies reporting on number of chest tubes (two vs. one) were all in the direction of increasing chronic post-surgical pain risk. The other surgery-related prognostic factors were either reported by very few studies or had inconsistent directions of effect.

In the sensitivity analyses, intercostal nerve block and sex lost significance, although the direction of effect remained the same. For the other prognostic factors, the sensitivity analyses were consistent with the main results. The results of the sensitivity analyses are summarised in online Supporting Information Tables S12–S14.

In the subgroup analyses, sex lost significance in the ≥ 50% video-assisted thoracic surgery and ≥ 50% regional anaesthesia subgroups. The other subgroup analyses, where applicable, were consistent with the main results. For neuropathic pain, no subgroup analyses were performed because none of the prognostic factors were reported by enough studies with neuropathic pain as chronic post-surgical

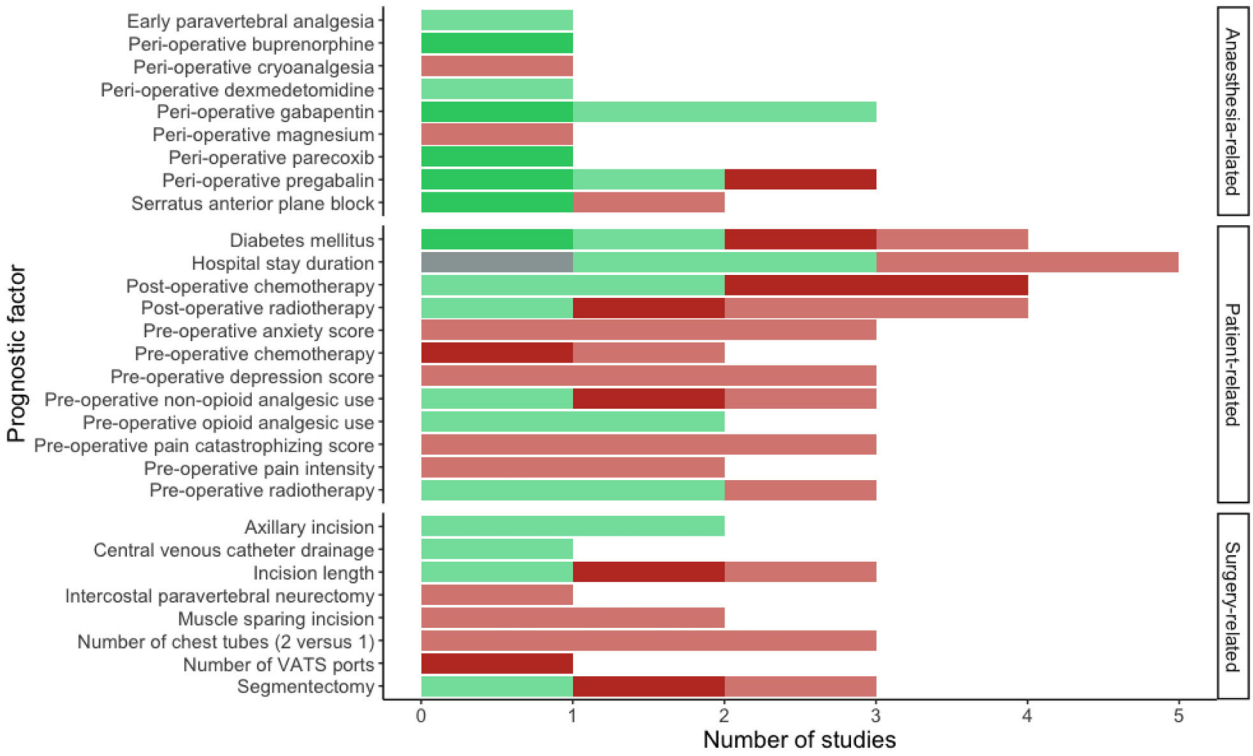

Figure 3 Direction of effect of prognostic factors not summarised with a meta-analysis. Dark green: lower chronic post-surgical pain risk (significant); light green: lower risk (non-significant); dark red: higher risk (significant); light red: higher risk (non-significant); grey: zero effect. VATS: video-assisted thoracic surgery.

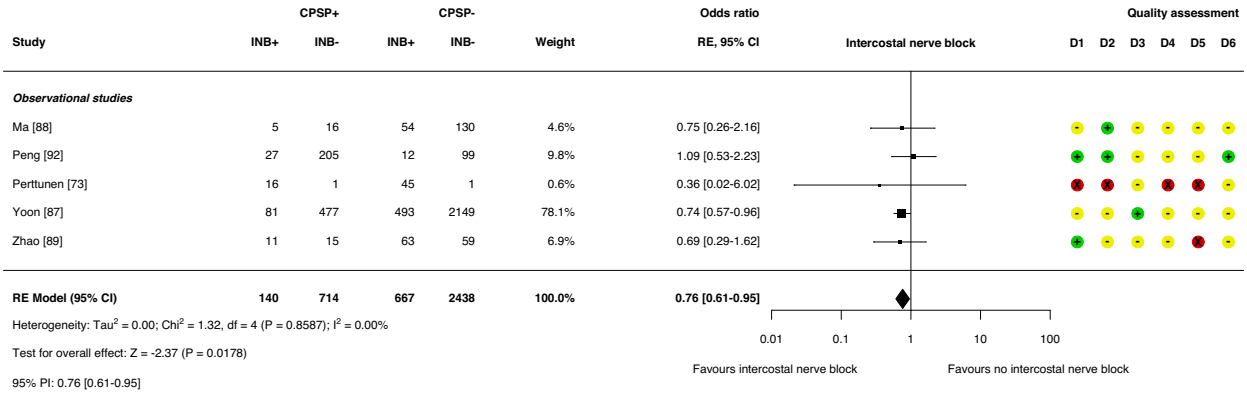

Figure 4 Forest plot for intercostal nerve block. D1, bias due to participation; D2, bias due to attrition; D3, bias due to prognostic factor measurement; D4, bias due to outcome measurement; D5, bias due to confounding; D6, bias in statistical analysis and reporting. CPSP, chronic post-surgical pain; INB, intercostal nerve block; RE, random effects; PI, prediction interval.

pain definition. The subgroup analyses results are summarised in online Supporting Information Tables S12–S14.

Meta-regression was performed for: follow-up time; proportion of females; proportion of video-assisted thoracic surgery; proportion with malignant disease; and proportion receiving regional anaesthesia for four prognostic factors: epidural analgesia; age; sex; and video-assisted thoracic surgery. The meta-regression for age with the proportion of females as covariate resulted in a change in mean difference (95%CI) of -0.2119 (-0.3712 to -0.0525), p = 0.009, for each percentage point increase in females. The other meta-regression analyses, where applicable, did not result in any covariates with a significant effect on the effect measures of the prognostic factors. The results of all meta-regression analyses are summarised in online Supporting Information Table S15.

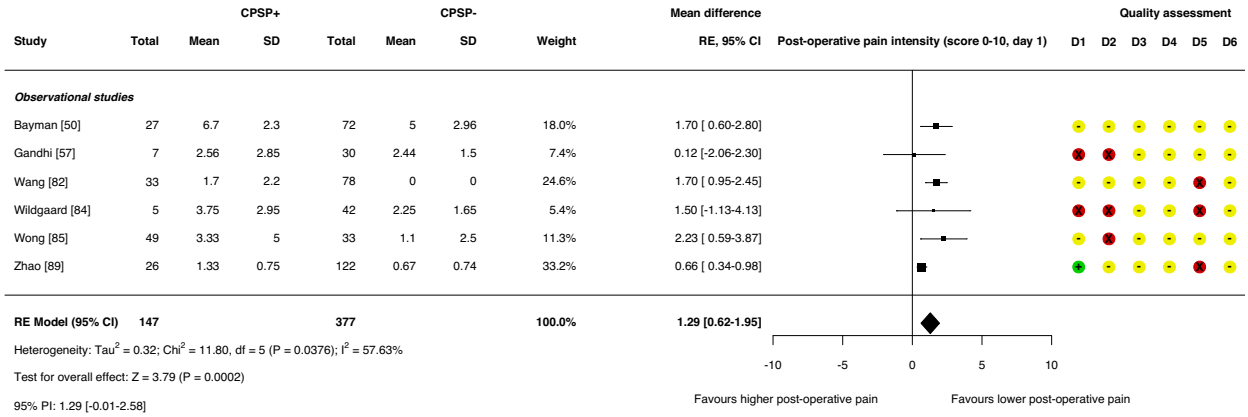

Figure 5 Forest plot for postoperative pain intensity (day 1). D1–D6 as per Fig. 4.

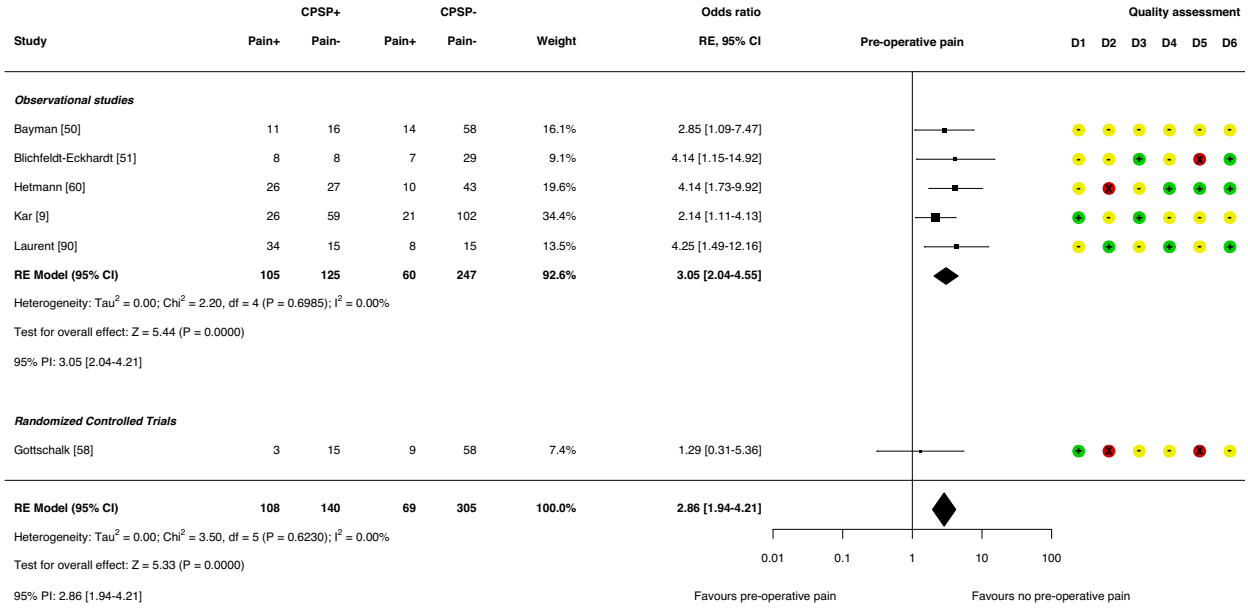

Figure 6 Forest plot for pre-operative pain. D1–D6 as per Fig. 4.

Assessment of potential publication bias was performed for age, epidural analgesia, sex and video-assisted thoracic surgery (online Supporting Information Figs. S33–S36). Testing for asymmetry of the funnel plots resulted in a p-value of 0.175 for age, 0.567 for epidural analgesia, 0.373 for sex and 0.723 for video-assisted thoracic surgery, indicating no present publication bias. The results of the certainty of evidence assessments are summarised in Table 2.

Discussion

This systematic review and meta-analysis was undertaken to identify all studies reporting prognostic factors for chronic post-surgical pain after lung or pleural surgery, and to summarise the evidence for each prognostic factor. We identified 45 prognostic factors in 56 studies, of which a meta-analysis was performed for 16 prognostic factors. Almost a third of the studies had a high risk of bias in the `confounding´ domain. The other five domains of the quality in prognostic studies tool had low rates of high risk [32]. Based on the conventional meta-analyses, pre-operative pain, higher postoperative pain intensity, female sex and longer surgery duration were associated with a higher chronic post-surgical pain risk, and intercostal nerve block and video-assisted thoracic surgery with a lower chronic post-surgical pain risk. While trial sequential analysis showed adequate power of the meta-analyses for intercostal nerve block, postoperative pain intensity, pre-

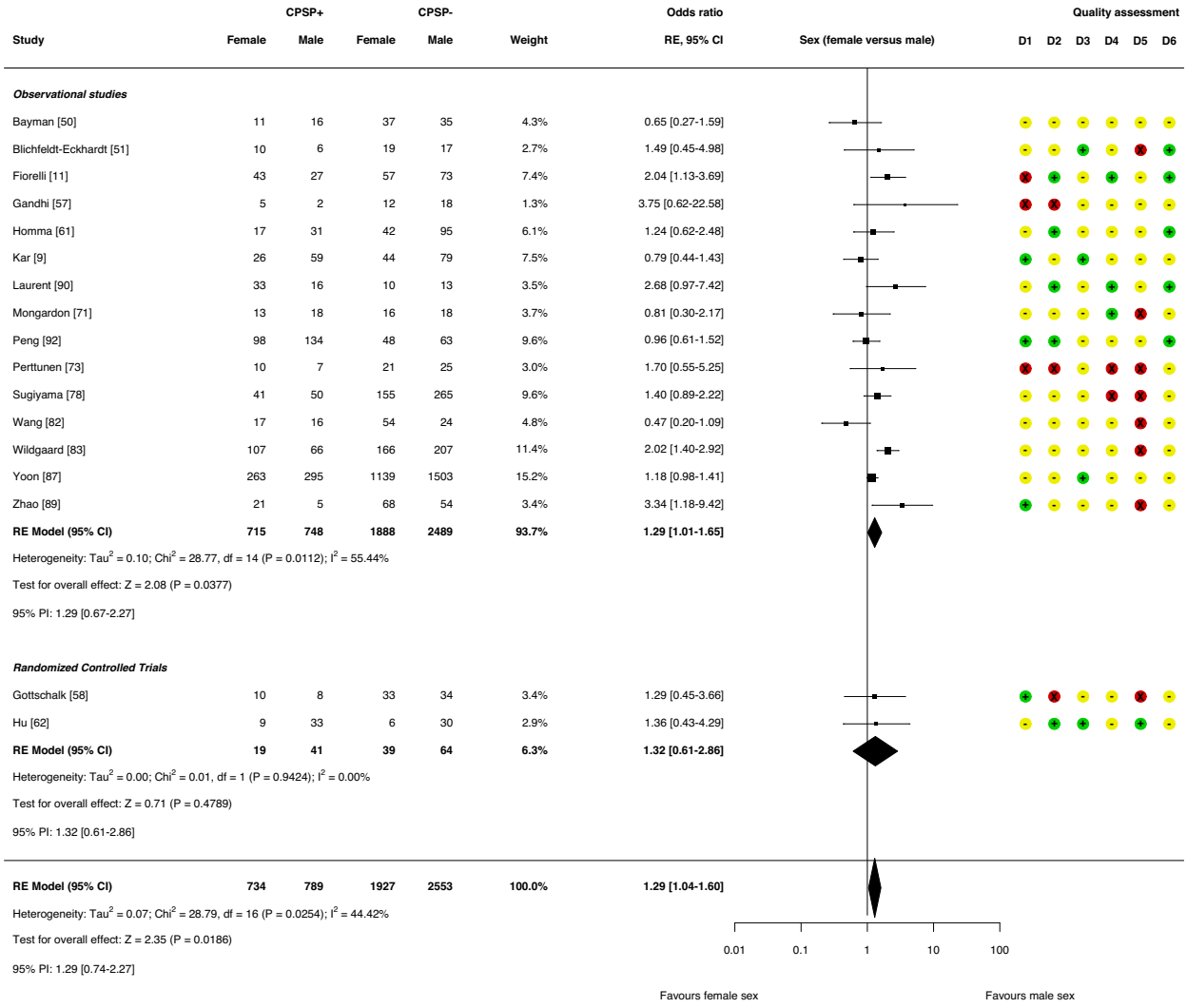

Figure 7 Forest plot for sex (female vs. male). D1–D6 as per Fig. 4.

operative pain, surgery duration and video-assisted thoracic surgery, this was not the case for sex. The certainty of evidence was high for pre-operative pain and video-assisted thoracic surgery, moderate for intercostal nerve block and surgery duration and low for postoperative pain intensity and sex. Meta-regression showed a significant effect of the proportion of females on the pooled effect measure of age. With an increase in the proportion of females, patients with chronic post-surgical pain were either on average older or patients without chronic post-surgical pain younger, which could explain part of the heterogeneity in the meta-analysis for age.

Two other systematic reviews and meta-analyses have been published that have some similarities with this study [25, 26]. Lim et al. pooled all types of thoracic surgery and found the following to be associated with chronic post-surgical pain after thoracic surgery: younger age; female sex; hypertension; pre-operative pain; moderate to severe acute postoperative pain; surgical approach (open thoracotomy); major procedure (bilobectomy, pneumonectomy, lobectomy plus wedge resection and pleurectomy); and wound complications [25]. Chen et al. pooled all types of video-assisted thoracic surgery and found associations with chronic post-surgical pain after such surgery with: female sex; younger age; higher postoperative pain intensity; and longer surgery duration [26]. While we did find the association with chronic post-surgical pain for pre-operative pain, postoperative pain intensity and surgical approach, age had no significant effect. For sex, the conventional meta-analysis also showed a significant effect in our study. However, trial sequential analysis reported inadequate power which

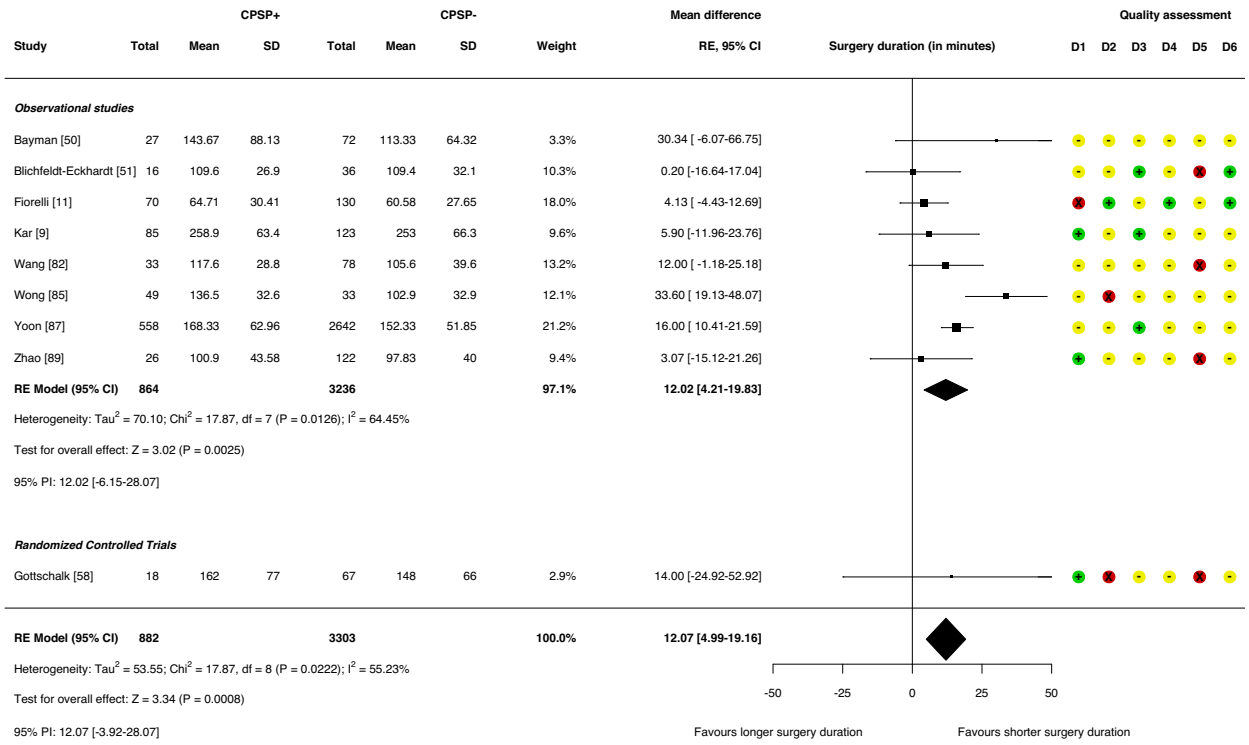

Figure 8 Forest plot for surgery duration (in minutes). D1–D6 as per Fig. 4.

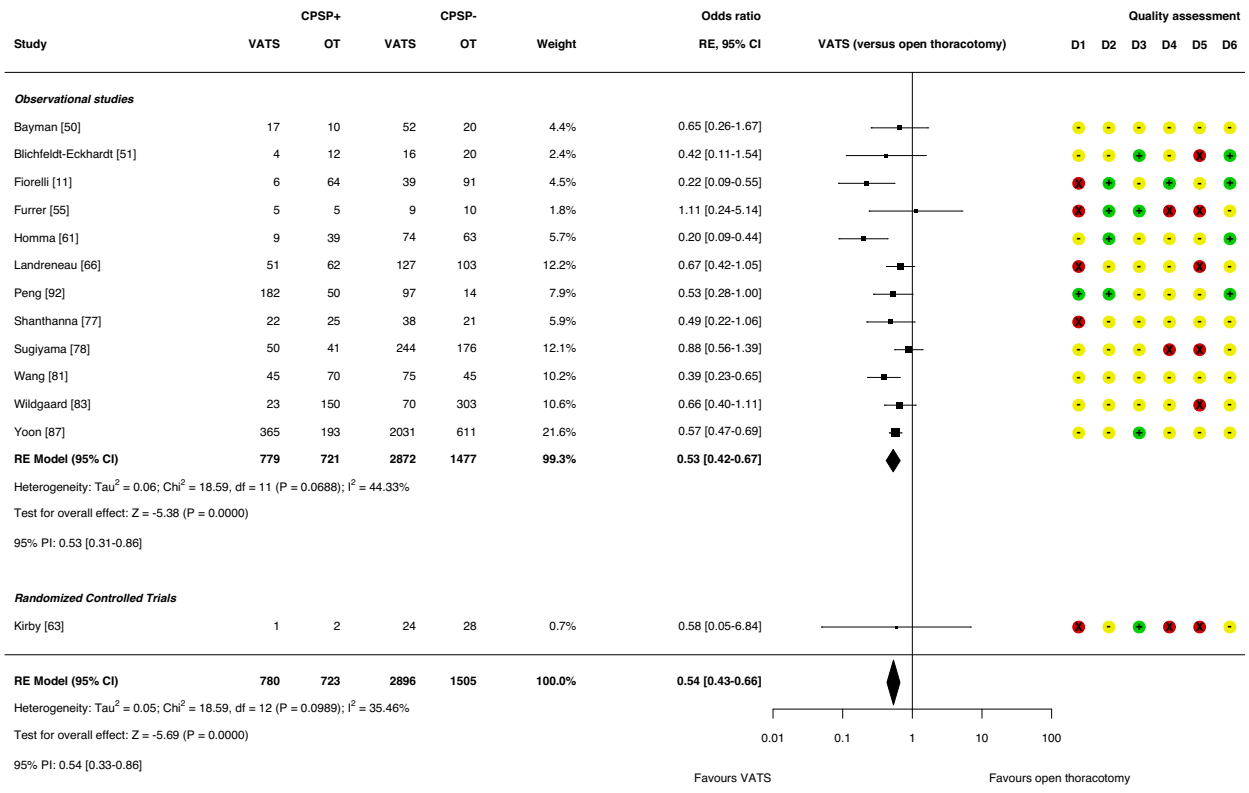

Figure 9 Forest plot for VATS (vs. open thoracotomy). D1–D6 as per Fig. 4. VATS: video-assisted thoracic surgery; OT: open thoracotomy.

reduced the certainty of evidence. Our study underlines the role of trial sequential analysis in meta-analyses because it helps to prevent fallacious conclusions. Unlike Lim et al. and Chen et al. [25, 26], we cannot conclude from the studies published so far that there is sufficient evidence to establish sex as a prognostic factor of chronic post-surgical pain after lung and pleural surgery. Our finding may guide future research and we think that further studies are needed to elucidate the role of sex in the development of persistent postoperative pain after lung or pleural surgery. Hypertension, major procedures and wound complications were not reported by enough included studies to assess them as prognostic factors. Finally, intercostal nerve block and surgery duration had a significant effect on chronic post-surgical pain in our study, while Lim et al. did not assess these factors and Chen et al. only did this for surgery duration. The differences in findings could be explained by studies with other thoracic surgery types that Lim et al. and Chen et al. included. For example, almost a third of the thoracic surgery studies Lim et al. included were cardiac surgery and Chen et al. also included studies on funnel chest surgery.

There are several strengths that distinguish our study from the others on this topic. First, no other meta-analysis has reported on prognostic factors specifically for chronic post-surgical pain after lung or pleural surgery. Thoracic surgery encompasses many types of heterogenous surgical procedures, with major differences in surgical technique. Differences in chronic post-surgical pain incidence have, for example, been observed between thoracotomy and sternotomy [104]. Different types of thoracic surgery are therefore likely to have a variety of pathways that cause chronic post-surgical pain and it makes sense to identify prognostic factors for specific types of thoracic surgery as has been done for cardiac surgery [27, 28]. Second, we used a variety of advanced statistical methods including trial sequential analysis, which is especially useful in the certainty of evidence assessment, considering the high rates of inflated type 1 and type 2 errors in meta-analyses [105, 106]. Third, the quality of the methodology in this study greatly benefitted from the rigorous guidance provided by the prognosis research strategy group [24]. Fourth, our analysis is more recent compared with that by Lim et al., since they searched until November 2019, and more complete as compared with Chen et al., since they included only 17 video-assisted thoracic surgery studies. Finally, we have prespecified our protocol both in a PROSPERO registration and a separate published protocol [30]. Smith and Carlisle emphasised the role of publishing the study protocol for transparency and minimising selective reporting bias in systematic reviews and meta-analyses [39], a notion that has been supported by others [107].

This study also has limitations worth considering, most notably the heterogeneity between studies for each prognostic factor. Although we conducted subgroup analyses and meta-regressions to identify sources of heterogeneity, much of the heterogeneity in the meta-analyses remained unexplained. Additionally, the required information size for some prognostic factors was inflated due to the correction for heterogeneity. Nevertheless, our results remain valid and relevant because we used a random-effects model to correct for between-study heterogeneity and age being the only prognostic factor with a high (> 75%) heterogeneity [38]. Another limitation is that a meta-analysis was not possible for many prognostic factors due to the limited number of studies reporting the same effect measure. Finally, even though five of the six quality assessment domains had low rates of high risk of bias, the study confounding domain was scored as high risk of bias in almost a third of the studies. This was addressed by incorporating the quality of the studies in our certainty of evidence assessment.

In summary, we have identified the presence of pre-operative pain, higher postoperative pain intensity and longer surgery duration as prognostic factors for developing chronic post-surgical pain after lung and pleural surgery. These findings are of added value for pre-operative clinical decision-making, peri-operative case consultations and clinical protocols to identify patients at risk of developing chronic post-surgical pain. In addition, these prognostic factors might serve as new targets for interventions to reduce the risk of developing chronic post-surgical pain. This entails optimising pre-operative pain before surgery; choosing video-assisted thoracic surgery whenever possible; considering intercostal nerve block when applicable; minimising surgery duration; and implementing standardised, multimodal analgesia in the immediate postoperative period – for which evidence-based guidelines on pain management are needed. A procedure-specific postoperative pain management guideline for video-assisted thoracic surgery was recently published [108]. In light of our results, we recommend similar guidelines be developed for other types of lung and pleural surgery. Finally, in contrast to other studies [25, 26], we do not think that the role of patient sex is clarified enough, and future studies are needed to confirm the impact of this possibly important factor.

Acknowledgements

This trial was registered on PROSPERO (CRD42021227888).

No competing interests declared.

References

1. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD, The IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain* 2019; **160**: 45–52.
2. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015; **156**: 1003–7.
3. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; **393**: 1537–46.
4. Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, Eschalier A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. *Pain* 2011; **152**: 74–81.
5. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013; **154**: 95–102.
6. Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. *Journal of Pain* 2014; **15**: 887–97.
7. Cregg R, Anwar S, Farquhar-Smith P. Persistent postsurgical pain. *Current Opinion in Supportive and Palliative Care* 2013; **7**: 144–52.
8. Kinney MA, Hooten WM, Cassivi SD, et al. Chronic postthoracotomy pain and health-related quality of life. *Annals of Thoracic Surgery* 2012; **93**: 1242–7.
9. Kar P, Sudheshna KD, Padmaja D, Pathy A, Gopinath R. Chronic pain following thoracotomy for lung surgeries: it's risk factors, prevalence, and impact on quality of life - a retrospective study. *Indian Journal of Anaesthesia* 2019; **63**: 368–74.
10. Peng Z, Li H, Zhang C, Qian X, Feng Z, Zhu S. A retrospective study of chronic post-surgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on quality of life. *PLoS One* 2014; **9**: e90014.
11. Fiorelli S, Cioffi L, Menna C, et al. Chronic pain after lung resection: risk factors, neuropathic pain, and quality of life. *Journal of Pain and Symptom Management* 2020; **60**: 326–35.
12. Loxe SC, de Mello LS, Camara L, et al. Chronic pain after lung transplantation and its impact on quality of life: a 4-year follow-up. *Transplantation Proceedings* 2020; **52**: 1388–93.
13. Blyth FM, March LM, Brnabic AJ, Cousins MJ. Chronic pain and frequent use of health care. *Pain* 2004; **111**: 51–8.
14. Blyth FM, March LM, Nicholas MK, Cousins MJ. Chronic pain, work performance and litigation. *Pain* 2003; **103**: 41–7.
15. van Leeuwen MT, Blyth FM, March LM, Nicholas MK, Cousins MJ. Chronic pain and reduced work effectiveness: the hidden cost to Australian employers. *European Journal of Pain* 2006; **10**: 161–6.
16. Parsons B, Schaefer C, Mann R, et al. Economic and humanistic burden of post-trauma and post-surgical neuropathic pain among adults in the United States. *Journal of Pain Research* 2013; **6**: 459–69.
17. Brown MR, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *British Journal of Pain* 2014; **8**: 139–53.
18. Huang A, Azam A, Segal S, et al. Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service. *Pain Management* 2016; **6**: 435–43.
19. Baker DW. History of the Joint Commission's Pain Standards: lessons for today's prescription opioid epidemic. *Journal of the American Medical Association* 2017; **317**: 1117–8.
20. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician* 2010; **13**: 401–35.
21. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *British Medical Journal* 2014; **348**: g1251.
22. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *British Medical Journal* 2013; **346**: e5595.
23. Altman DG. Systematic reviews of evaluations of prognostic variables. *British Medical Journal* 2001; **323**: 224–8.
24. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *British Medical Journal* 2019; **364**: k4597.
25. Lim J, Chen D, McNicol E, et al. Risk factors for persistent pain after breast and thoracic surgeries: a systematic literature review and meta-analysis. *Pain* 2022; **163**: 3–20.
26. Chen WC, Bai YY, Zhang LH, Liu YB, Liu CY, Liang JW, He HF. Prevalence and predictors of chronic postsurgical pain after video-assisted thoracoscopic surgery: a systematic review and meta-analysis. *Pain and Therapy* 2023; **12**: 117–39.
27. Bae J, Shin S. [Factors related to persistent postoperative pain after cardiac surgery: a systematic review and meta-analysis]. *Journal of Korean Academy of Nursing* 2020; **50**: 159–77.
28. Guimaraes-Pereira L, Reis P, Abelha F, Azevedo LF, Castro-Lopes JM. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 2017; **158**: 1869–85.
29. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Journal of Clinical Epidemiology* 2021; **134**: 178–89.
30. Clephas PRD, Hoeks SE, Trivella M, et al. Prognostic factors for chronic post-surgical pain after lung or pleural surgery: a protocol for a systematic review and meta-analysis. *British Medical Journal Open* 2021; **11**: e051554.
31. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. *Journal of the Medical Library Association* 2018; **106**: 531–41.
32. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Annals of Internal Medicine* 2006; **144**: 427–37.
33. Wan X, Wang W, Liu J, 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.
34. Jackson D, Turner R. Power analysis for random-effects meta-analysis. *Research Synthesis Methods* 2017; **8**: 290–302.
35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; **7**: 177–88.
36. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *British Medical Journal* 2011; **342**: d549.
37. Int Hout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *British Medical Journal Open* 2016; **6**: e010247.
38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003; **327**: 557–60.
39. Smith AF, Carlisle J. Reviews, systematic reviews and Anaesthesia. *Anaesthesia* 2015; **70**: 644–50.
40. Clephas PRD, Kranke P, Heesen M. How to perform and write a trial sequential analysis. *Anaesthesia* 2023; **78**: 381–4.
41. Clephas PRD, Heesen M. Interpretation of meta-analyses. *Interventional Pain Medicine* 2022; **1**: 100120.

42. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2021. www.training.cochrane.org/handbook (accessed 20/02/2021).
43. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *British Medical Journal* 2001; **323**: 101–5.
44. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *Journal of Clinical Epidemiology* 2005; **58**: 894–901.
45. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006; **25**: 3443–57.
46. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. *Statistics in Medicine* 2015; **34**: 343–60.
47. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* 2010; **36**: 1–48.
48. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA), 2011. www.ctu.dk/tsa (accessed 06/06/2022).
49. Foroutan F, Guyatt G, Zuk V, et al. GRADE Guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *Journal of Clinical Epidemiology* 2020; **121**: 62–70.
50. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A prospective study of chronic pain after thoracic surgery. *Anesthesiology* 2017; **126**: 938–51.
51. Blichfeldt-Eckhardt MR, Andersen C, Ording H, Licht PB, Toft P. From acute to chronic pain after thoracic surgery: the significance of different components of the acute pain response. *Journal of Pain Research* 2018; **11**: 1541–8.
52. Borys M, Hanych A, Czuczwar M. Paravertebral block versus preemptive ketamine effect on pain intensity after posterolateral thoracotomies: a randomized controlled trial. *Journal of Clinical Medicine* 2020; **9**: 793.
53. Brulotte V, Ruel MM, Lafontaine E, Chouinard P, Girard F. Impact of pregabalin on the occurrence of postthoracotomy pain syndrome: a randomized trial. *Regional Anesthesia and Pain Medicine* 2015; **40**: 262–9.
54. Chumbley GM, Thompson L, Swatman JE, Urch C. Ketamine infusion for 96 hr after thoracotomy: effects on acute and persistent pain. *European Journal of Pain* 2019; **23**: 985–93.
55. Furrer M, Rechsteiner R, Eigenmann V, Signer C, Althaus U, Ris HB. Thoracotomy and thoracoscopy: postoperative pulmonary function, pain and chest wall complaints. *European Journal of Cardio-Thoracic Surgery* 1997; **12**: 82–7.
56. Gaber S, Saleh E, Elshaikh S, Reyad R, Elramly M, Mourad I, Abdel Fattah M. Role of perioperative pregabalin in the management of acute and chronic post-thoracotomy pain. *Open Access Macedonian Journal of Medical Sciences* 2019; **7**: 1974–8.
57. Gandhi W, Pomares FB, Naso L, Asenjo JF, Schweinhardt P. Neuropathic pain after thoracotomy: tracking signs and symptoms before and at monthly intervals following surgery. *European Journal of Pain* 2020; **24**: 1269–89.
58. Gottschalk A, Ochroch EA. Clinical and demographic characteristics of patients with chronic pain after major thoracotomy. *Clinical Journal of Pain* 2008; **24**: 708–16.
59. Grosen K, Drewes AM, Hojsgaard A, Pfeiffer-Jensen M, Hjortdal VE, Pilegaard HK. Perioperative gabapentin for the prevention of persistent pain after thoracotomy: a randomized controlled trial. *European Journal of Cardio-Thoracic Surgery* 2014; **46**: 76–85.
60. Hetmann F, Kongsgaard UE, Sandvik L, Schou-Bredal I. Prevalence and predictors of persistent post-surgical pain 12 months after thoracotomy. *Acta Anaesthesiologica Scandinavica* 2015; **59**: 740–8.
61. Homma T, Doki Y, Yamamoto Y, Ojima T, Shimada Y, Kitamura N, Yoshimura N. Risk factors of neuropathic pain after thoracic surgery. *Journal of Thoracic Disease* 2018; **10**: 2898–907.
62. Hu J, Liao Q, Zhang F, Tong J, Ouyang W. Chronic postthoracotomy pain and perioperative ketamine infusion. *Journal of Pain and Palliative Care Pharmacotherapy* 2014; **28**: 117–21.
63. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy—video-assisted thoracic surgery versus muscle-sparing thoracotomy: a randomized trial. *Journal of Thoracic and Cardiovascular Surgery* 1995; **109**: 997–1001.
64. Kosucu M, Tugcugil E, Erturk E, et al. The effects of the pre-emptive oral gabapentin on post-anesthesia recovery criteria, acute post-thoracotomy pain and development of chronicity in pain with benign thoracotomy operations. *Turkish Journal of Thoracic and Cardiovascular Surgery* 2014; **22**: 389–96.
65. Kozar S, Maric S, Jankovic VN. Development of post-thoracotomy pain syndrome in patients undergoing lung surgery - comparison of thoracic paravertebral and epidural analgesia. *Periodicum Biologorum* 2011; **113**: 229–33.
66. Landreneau RJ, Mack MJ, Hazelrigg SR, et al. Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. *Journal of Thoracic and Cardiovascular Surgery* 1994; **107**: 1079–85.
67. Landreneau RJ, Pigula F, Luketich JD, et al. Acute and chronic morbidity differences between muscle-sparing and standard lateral thoracotomies. *Journal of Thoracic and Cardiovascular Surgery* 1996; **112**: 1346–50.
68. Lee CY, Narm KS, Lee JG, et al. A prospective randomized trial of continuous paravertebral infusion versus intravenous patient-controlled analgesia after thoracoscopic lobectomy for lung cancer. *Journal of Thoracic Disease* 2018; **10**: 3814–23.
69. Mendola C, Cammarota G, Netto R, et al. S(+)-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. *Minerva Anestesiologica* 2012; **78**: 757–66.
70. Miyazaki T, Sakai T, Sato S, et al. Is pain catastrophizing scale useful for predicting post-thoracotomy pain after lung cancer surgery? *Acta Medica Nagasakiensia* 2019; **63**: 41–8.
71. Mongardon N, Pinton-Gonnet C, Szekely B, Michel-Cherqui M, Dreyfus JF, Fischler M. Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clinical Journal of Pain* 2011; **27**: 677–81.
72. Nomori H, Horio H, Fuyuno G, Kobayashi R. Non-serratus-sparing antero-axillary thoracotomy with disconnection of anterior rib cartilage. Improvement in postoperative pulmonary function and pain in comparison to posterolateral thoracotomy. *Chest* 1997; **111**: 572–6.
73. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiologica Scandinavica* 1999; **43**: 563–7.
74. Reyad RM, Shaker EH, Ghobrial HZ, et al. The impact of ultrasound-guided continuous serratus anterior plane block versus intravenous patient-controlled analgesia on the incidence and severity of post-thoracotomy pain syndrome: a randomized, controlled study. *European Journal of Pain* 2020; **24**: 159–70.
75. Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? *Interactive Cardiovascular and Thoracic Surgery* 2009; **9**: 999–1002.
76. Senturk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesthesia and Analgesia* 2002; **94**: 11–5.

77. Shanthanna H, Aboutouk D, Poon E, Cheng J, Finley C, Paul J, Thabane L. A retrospective study of open thoracotomies versus thoracoscopic surgeries for persistent postthoracotomy pain. *Journal of Clinical Anesthesia* 2016; **35**: 215–20.
78. Sugiyama Y, Iida H, Amaya F, et al. Prevalence of chronic postsurgical pain after thoracotomy and total knee arthroplasty: a retrospective multicenter study in Japan (Japanese Study Group of Subacute Postoperative Pain). *Journal of Anesthesia* 2018; **32**: 434–8.
79. Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* 2006; **105**: 111–9.
80. Tunc M, Cinar D, Sahin S, Sazak H, Kose SK. The effects of pre-emptive pregabalin on post-thoracotomy pain and epidural analgesia. *Turk Gogus Kalp Damar Cerrahisi Dergisi-Turkish Journal of Thoracic and Cardiovascular Surgery* 2014; **22**: 129–37.
81. Wang H, Li S, Liang N, Liu W, Liu H, Liu H. Postoperative pain experiences in Chinese adult patients after thoracotomy and video-assisted thoracic surgery. *Journal of Clinical Nursing* 2017; **26**: 2744–54.
82. Wang S, Li Y, Fei M, Zhang H, Wang J. Clinical analysis of the effects of different anesthesia and analgesia methods on chronic postsurgical pain in patients with Uniportal video-assisted lung surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2020; **34**: 987–91.
83. Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. *Acta Anaesthesiologica Scandinavica* 2011; **55**: 60–8.
84. Wildgaard K, Ringsted TK, Hansen HJ, Petersen RH, Kehlet H. Persistent postsurgical pain after video-assisted thoracic surgery - an observational study. *Acta Anaesthesiologica Scandinavica* 2016; **60**: 650–8.
85. Wong J, Cooper J, Thomas R, Langford R, Anwar S. Persistent postsurgical pain following thoracotomy: a comparison of thoracic epidural and paravertebral blockade as preventive analgesia. *Pain Medicine* 2019; **20**: 1796–802.
86. Yeung J, Middleton L, Tryposkiadis K, et al. Randomised controlled trial to investigate the effectiveness of thoracic epidural and paravertebral blockade in reducing chronic post-thoracotomy pain (TOPIC): a pilot study to assess feasibility of a large multicentre trial. *British Medical Journal Open* 2019; **9**: e023679.
87. Yoon S, Hong WP, Joo H, Kim H, Park S, Bahk JH, Lee HJ. Long-term incidence of chronic postsurgical pain after thoracic surgery for lung cancer: a 10-year single-center retrospective study. *Regional Anesthesia and Pain Medicine* 2020; **45**: 331–6.
88. Ma H, Song X, Li J, Wu G. Postoperative pain control with continuous paravertebral nerve block and intercostal nerve block after two-port video-assisted thoracic surgery. *Wideochirurgia i inne techniki małoinwazyjne* 2021; **16**: 273–81.
89. Zhao H, Wu Y, Zhang X, Feng Y. The effect of preoperative serratus anterior muscle plane block on persistent postsurgical pain after video-assisted thoracic surgery: a retrospective cohort study. *Clinical Journal of Pain* 2021; **37**: 759–65.
90. Laurent Q, Michel-Cherqui M, Szekely B, et al. Prevalence, characteristics and preoperative predictors of chronic pain after double-lung transplantation: a prospective cohort study. *Journal of Cardiothoracic and Vascular Anesthesia* 2022; **36**: 500–9.
91. Wang G, He M, Ji XL, Wang XL, Feng Y. Identifying patients at high risk of chronic pain after video-assisted thoracoscopic surgery using thermal quantitative sensory testing. *Journal of Cardiothoracic and Vascular Anesthesia* 2022; **36**: 2406–11.
92. Peng J, Wang Z, Ma L, et al. Incidence and influencing factors of chronic Postthoracotomy pain in lung tumor patients. *Journal of Healthcare Engineering* 2022; **2022**: 7584481.
93. Duale C, Sibaud F, Guastella V, et al. Perioperative ketamine does not prevent chronic pain after thoracotomy. *European Journal of Pain* 2009; **13**: 497–505.
94. Kinney MA, Mantilla CB, Carns PE, et al. Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. *Pain Practice* 2012; **12**: 175–83.
95. Wei S, Zhang G, Ma J, Nong L, Zhang J, Zhong W, Cui J. Randomized controlled trial of an alternative drainage strategy vs routine chest tube insertion for postoperative pain after thoracoscopic wedge resection. *BMC Anesthesiology* 2022; **22**: 27.
96. Jin J, Du X, Min S, Liu L. Comparison of chronic postsurgical pain between single-port and multi-port video-assisted thoracoscopic pulmonary resection: a prospective study. *Thoracic and Cardiovascular Surgeon* 2022; **70**: 430–8.
97. Abd-Elshafy SK, Abdallal F, Kamel EZ, et al. Paravertebral dexmedetomidine in video-assisted thoracic surgeries for acute and chronic pain prevention. *Pain Physician* 2019; **22**: 271–80.
98. Kamalanathan K, Knight T, Rasburn N, Joshi N, Molyneux M. Early versus late paravertebral block for analgesia in video-assisted thoracoscopic lung resection. A double-blind, randomized, placebo-controlled trial. *Journal of Cardiothoracic and Vascular Anesthesia* 2019; **33**: 453–9.
99. Koryllos A, Althaus A, Poels M, et al. Impact of intercostal paravertebral neurectomy on post thoracotomy pain syndrome after thoracotomy in lung cancer patients: a randomized controlled trial. *Journal of Thoracic Disease* 2016; **8**: 2427–33.
100. Lee JH, Yang WD, Han SY, et al. Effect of epidural magnesium on the incidence of chronic postoperative pain after video-assisted thoracic surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2012; **26**: 1055–9.
101. Ling XM, Fang F, Zhang XG, Ding M, Liu QA, Cang J. Effect of parecoxib combined with thoracic epidural analgesia on pain after thoracotomy. *Journal of Thoracic Disease* 2016; **8**: 880–7.
102. Mercieri M, Palmisani S, De Blasi RA, et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. *British Journal of Anaesthesia* 2017; **119**: 792–802.
103. Gwak MS, Yang M, Hahm TS, Cho HS, Cho CH, Song JG. Effect of cryoanalgesia combined with intravenous continuous analgesia in thoracotomy patients. *Journal of Korean Medical Science* 2004; **19**: 74–8.
104. Minami K, Kabata D, Kakuta T, Fukushima S, Fujita T, Yoshitani K, Ohnishi Y. Association between sternotomy versus thoracotomy and the prevalence and severity of chronic postsurgical pain after mitral valve repair: an observational cohort study. *Journal of Cardiothoracic and Vascular Anesthesia* 2021; **35**: 2937–44.
105. Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic reviews of anesthesiologic interventions reported as statistically significant: problems with power, precision, and type 1 error protection. *Anesthesia and Analgesia* 2015; **121**: 1611–22.
106. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. *British Medical Journal Open* 2016; **6**: e011890.

107. Stewart L, Moher D, Shekelle P. Why prospective registration of systematic reviews makes sense. *Systematic Reviews* 2012; **1**: 7.
108. Feray S, Lubach J, Joshi GP, et al. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia* 2022; **77**: 311–25.

Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Systematic search for each database.

Figure S1. Forest plot for epidural analgesia.

Figure S2. Forest plot for intercostal nerve block.

Figure S3. Forest plot for paravertebral analgesia.

Figure S4. Forest plot for peri-operative ketamine.

Figure S5. Forest plot for age.

Figure S6. Forest plot for ASA score (III/IV versus I/II).

Figure S7. Forest plot for BMI.

Figure S8. Forest plot for malignant diseases.

Figure S9. Forest plot for postoperative pain intensity (score 0–10, day 1).

Figure S10. Forest plot for pre-operative pain.

Figure S11. Forest plot for sex (female versus male).

Figure S12. Forest plot for smoking.

Figure S13. Forest plot for chest tube duration (in days).

Figure S14. Forest plot for lobectomy.

Figure S15. Forest plot for surgery duration (in minutes).

Figure S16. Forest plot for VATS (versus open thoracotomy).

Figure S17. Trial sequential analysis plot for epidural analgesia.

Figure S18. Trial sequential analysis plot for intercostal nerve block.

Figure S19. Trial sequential analysis plot for paravertebral analgesia.

Figure S20. Trial sequential analysis plot for peri-operative ketamine.

Figure S21. Trial sequential analysis plot for age.

Figure S22. Trial sequential analysis plot for ASA score (III/IV versus I/II).

Figure S23. Trial sequential analysis plot for BMI.

Figure S24. Trial sequential analysis plot for malignant diseases.

Figure S25. Trial sequential analysis plot for postoperative pain intensity (score 0–10, day 1).

Figure S26. Trial sequential analysis plot for pre-operative pain.

Figure S27. Trial sequential analysis plot for sex (female versus male).

Figure S28. Trial sequential analysis plot for smoking.

Figure S29. Trial sequential analysis plot for chest tube duration.

Figure S30. Trial sequential analysis plot for lobectomy.

Figure S31. Trial sequential analysis plot for surgery duration.

Figure S32. Trial sequential analysis plot for VATS (versus open thoracotomy)

Figure S33. Funnel plot for epidural analgesia.

Figure S34. Funnel plot for age.

Figure S35. Funnel plot for sex.

Figure S36. Funnel plot for VATS.

Table S1. Characteristics of the included studies.

Table S2. Risk of bias assessment.

Table S3. Anaesthesia-related prognostic factors summarised without meta-analysis.

Table S4. Patient-related prognostic factors summarised without meta-analysis.

Table S5. Surgery-related prognostic factors summarised without meta-analysis.

Table S6. Anaesthesia-related prognostic factors summarised with meta-analysis.

Table S7. Patient-related prognostic factors summarised with meta-analysis.

Table S8. Surgery-related prognostic factors summarised with meta-analysis.

Table S9. Direction of effect for anaesthesia-related prognostic factors summarised without meta-analysis.

Table S10. Direction of effect for anaesthesia-related prognostic factors summarised without meta-analysis.

Table S11. Direction of effect for surgery-related prognostic factors summarised without meta-analysis.

Table S12. Meta-analysis results for anaesthesia-related prognostic factors.

Table S13. Meta-analysis results for patient-related prognostic factors.

Table S14. Meta-analysis results for surgery-related prognostic factors.

Table S15. Meta-regression results.