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ORIGINAL RESEARCH

Prevalence and Predictors of Chronic Postsurgical Pain After Video-Assisted Thoracoscopic Surgery: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Determining the prevalence of chronic postsurgical pain (CPSP) after video-assisted thoracoscopic surgery (VATS) and identifying CPSP predictors should improve the prognosis of patients undergoing VATS. Although several studies have investigated predictors of CPSP after VATS, there were significant dissimilarities in the findings due to the confounding of predictors.

Methods: PubMed, Cochrane, MEDLINE, Web of Science, Chinese Biomedical Literature, and China National Knowledge Infrastructure databases were comprehensively searched using the Medical Subject Headings terms "pain, postoperative," "thoracic surgery, video-assisted," and all related free terms from inception until March 27, 2022. The Stata metaprop package was used to comprehensively analyze the incidence of CPSP following VATS. Furthermore, the pooled odds ratios (OR) or the standardized mean differences (SMD) and their corresponding 95% confidence intervals (95% CI) were calculated, and qualitative analyses were performed for predictors that could not be assessed quantitatively to evaluate the effects of the included risk factors on the occurrence of CPSP. Unadjusted odds ratios were utilized to consider the impact of non-significant estimates if the original study did not report them.

Results: Of the 4302 studies, 183 were considered eligible, and 17 were finally included in this study. The overall incidence of CPSP after VATS was 35.3% (95% CI 27.1–43.5%). The qualitative synthesis results revealed that female sex, age, and acute postoperative pain were definite predictors of CPSP after VATS. The number of ports, operation time, duration of drainage, and insufficient analgesia were also considered predictors. Consistent, quantitative synthesis results also showed that the aforementioned predictors were closely related to the occurrence of CPSP after VATS. Only by quantitative analysis, postoperative chemotherapy and an educational level less than junior school were also risk factors for CPSP. Other predictors

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displayed no evidence or unclear evidence of association with CPSP after VATS.
Conclusion: This study preliminarily determined the incidence of CPSP after VATS based on the existing literature. Female sex, age, and acute pain were identified as risk factors for CPSP after VATS, and other potential risk factors were also identified and analyzed. However, as a result of the inclusion of retrospective studies and inevitable limitations in this systematic review and meta-analysis, the results of this study still need to be verified by large-scale prospective clinical studies.
Trial Registration: CRD42022323179.

Keywords: Chronic postsurgical pain; Prevalence; Risk factors; Video-assisted thoracoscopic surgery

Key Summary Points

This study provides a comprehensive synthesis of the incidence of chronic postsurgical pain after video-assisted thoracoscopic surgery.

Female sex, age, and acute postoperative pain were predictors of chronic postsurgical pain development.

The study also revealed several potential risk factors for chronic postsurgical pain after video-assisted thoracoscopic surgery, including number of ports, operation time, duration of drainage, and insufficient analgesia.

Careful assessment of patients undergoing video-assisted thoracoscopic surgery with predictors of chronic postsurgical pain is required.

INTRODUCTION

Considering the notable increase in surgical volumes worldwide, there is growing recognition of the burden posed by chronic postsurgical pain (CPSP) [1, 2]. Currently, CPSP is far more common and excruciating than previously considered [3, 4]. The incidence of CPSP is highly variable depending on the type of surgery, with a 5–65% incidence rate following thoracic surgery [5, 6]. Although it has been reported that there is a lower incidence of CPSP after video-assisted thoracoscopic surgery (VATS) than after open thoracotomy [7], VATS has been widely used as an alternative to open thoracotomy since its introduction into clinical practice [8]. Therefore, the incidence of CPSP after VATS has great potential. Moreover, any occurrence of CPSP after VATS has a notable effect on patients' quality of life, with considerable effects on the healthcare system and socioeconomic costs [5, 9].

Estimates of the prevalence of CPSP following VATS vary widely (7.7–50%), presumably because of differences in definitions and postoperative follow-up periods and the small sample sizes of published studies [10]. In recent years, several studies have evaluated CPSP after thoracoscopic surgery, although significant controversy still exists surrounding their findings [10, 11]. Furthermore, the etiology of CPSP after VATS is multifactorial and may involve both patient- and treatment-related factors [12]. Although multiple retrospective studies have investigated the predictors of CPSP after VATS, there were significant dissimilarities due to confounding of the predictors assessed in these studies, leading to inconclusive results. More notably, some studies on predictors of CPSP after VATS did not report effect estimates for nonsignificant predictors or predictors that were significant in the univariate analysis although nonsignificant in the multivariate analysis [12]. This may have led to the exaggeration of existing predictors and neglect of potential predictors.

Elucidating the incidence of CPSP after VATS, accurately identifying predictors, and obtaining a precise understanding of the independent role of each predictor may help clinicians better recognize patients at risk of CPSP. It may also facilitate the early implementation of effective interventions, which is crucial in reducing the occurrence of CPSP. Accordingly, this study aimed to evaluate the incidence of CPSP after VATS and identify its potential predictors, which may help improve the prognosis of high-risk patients.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [14] guidelines (registration CRD42022323179). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search Strategy

Two reviewers (WC and YB) conducted an independent systematic search of the PubMed, Cochrane, Medline, Web of Science, Chinese Biomedical Literature (CBM), and China National Knowledge Infrastructure (CNKI) databases from their inception until March 27, 2022, with no restrictions on publication date. Potential studies were examined by employing a search strategy for the Medical Subject Headings terms "pain, postoperative," "thoracic surgery, video-assisted," and all related free terms. See the Supplementary Methods in the electronic Supplementary Material for the detailed search methodologies and procedures. In addition, we performed a detailed manual examination of the reference list of each study and associated systematic reviews to identify other potentially eligible studies. Any dispute in the process of study inclusion was resolved by a third party (HFH) after consultation between all parties.

Study Selection Criteria

Inclusion Criteria

This meta-analysis considered studies that (1) involved patients who underwent VATS, regardless of race, sex, age, or disease type; (2) evaluated the predictors of CPSP after VATS, such as basic, disease, surgical, and anesthesia information; (3) performed multivariate or univariate analysis involving predictors of CPSP after VATS; and (4) were retrospectively or prospectively conducted in Chinese or English.

Exclusion Criteria

We excluded studies (1) involving thoracotomy or VATS combined with thoracotomy, including anterolateral thoracotomy, posterolateral thoracotomy, and sternotomy; (2) from which relevant data could not be extracted; (3) involving a postoperative follow-up period of less than 2 months and that could not qualify for a valid diagnosis of CPSP; and (4) that were case reports, reviews, conferences, letters, surveys, or satisfaction studies.

Data Extraction and Quality Assessment

Data were independently extracted by two investigators (WC and YB) and crosschecked. The prevalence or incidence values, as well as any reported risk factors or predictors of CPSP after VATS, were recorded. Detailed data extraction is as follows: (1) basic information, including the first author, publication year, and country; (2) study characteristics, including study type, sex ratio, age, sample size, primary diagnosis, outcome measure instruments, and follow-up period; and (3) incidence of CPSP and predictors, including the results of multivariate (OR) and univariate (uOR) analyses. If the univariate analysis result was unavailable, uOR was calculated via a 2×2 table calculation [15]. Among them, the results based on aOR synthesis are independent. During the process of data extraction, differences of opinion were resolved via consensus between both investigators or with third party (JL) consultation.

The quality of the studies included in this meta-analysis was assessed by the two examiners on the basis of the Newcastle–Ottawa Scale (NOS) [16, 17]. The NOS score was qualitatively evaluated with respect to selection, comparison, and outcome/exposure of studies, with nine entries and 1 point per entry. The higher the NOS score, the higher the quality of the literature. Studies with a NOS score of less than 5

points were rejected.

Qualitative Synthesis

All included studies were used for the primary qualitative analysis of the results. Considering the methodological quality and number of corresponding studies, each identified predictor was flagged as definite, likely, unclear, or not a predictor [18]. The criteria were as follows: definite, at least three studies with NOS $\geq$ 7 showed positive results; likely, two studies with NOS $\geq$ 7 revealed positive results; not a predictor, at least two studies with NOS $\geq$ 7 indicated negative results without any positive results; unclear, other cases.

Quantitative Synthesis and Statistical Analyses

The same predictors from two or more studies were quantified. Meta-analysis of the extracted data was performed using Stata 14.0 (Stata Corporation, College Station, TX, USA). First, the χ^2 test was used to analyze the heterogeneity among the results of the included studies. If I^2 was less than 50% and P was greater than 0.1, there was no significant difference in heterogeneity, and a fixed-effects model was used. In contrast, if I^2 was at least 50% and P was less than 0.1, there was a significant difference in heterogeneity, and a random-effects model was adopted. Consequential clinical heterogeneity was analyzed separately using subgroup, sensitivity, or descriptive analyses. Risk estimates, both adjusted and unadjusted, were calculated using the odds ratio (OR), and the null hypothesis of indifference was rejected if the P value was less than 0.05, or the 95% confidence interval (CI) for the risk estimate did not include 1. Continuous variables in the characteristic data were assessed as the mean difference (MD) or standardized MD (SMD). The Stata metaprop command was used for pooling to merge single-group rates. Furthermore, to assess the risk of publication bias in this study, funnel plots were used to demonstrate publication bias [19] and were quantified using Egger's linear regression by identifying asymmetries. The effect of publication bias on the robustness of the results was estimated using the trim-and-fill method.

RESULTS

Included Studies

The study retrieved 4302 articles from the PUBMED, Medline, Web of Science, CBM, and CNKI databases. After 1336 duplicate studies were removed, 2966 studies were retained pending title and abstract screening. Thereafter, 183 records were carefully reviewed to ensure compliance with the inclusion criteria. Ultimately, 17 studies [10–12, 20–33], comprising 10,525 patients who underwent VATS, were included in this study (Fig. 1).

Study Characteristics

The main characteristics of the included studies are summarized in Table 1.

Of the 17 included studies, 3 were prospective and 14 were retrospective. Fourteen of the studies were conducted in China; the rest were conducted in South Korea, Italy, and Israel. Of the 10,525 patients who underwent VATS, 2526 had CPSP and 7999 did not have CPSP. The primary diagnosis of the included patients was most commonly lung cancer, accompanied by pectus excavatum and spontaneous pneumothorax. The follow-up period was usually 3 months or more; only three studies included a 2-month follow-up period, owing to historical differences in the definition of CPSP [4, 34].

Methodological Quality

The methodological quality of the included studies varied, with NOS scores ranging from 5 to 8 out of 9 (median 7) (see Table S1 in the electronic Supplementary Material). The included studies that scored low in the selection and outcome/exposure categories. The most common sources of risk included the lack of a prospective design, inadequate matching for important confounders, and insufficient

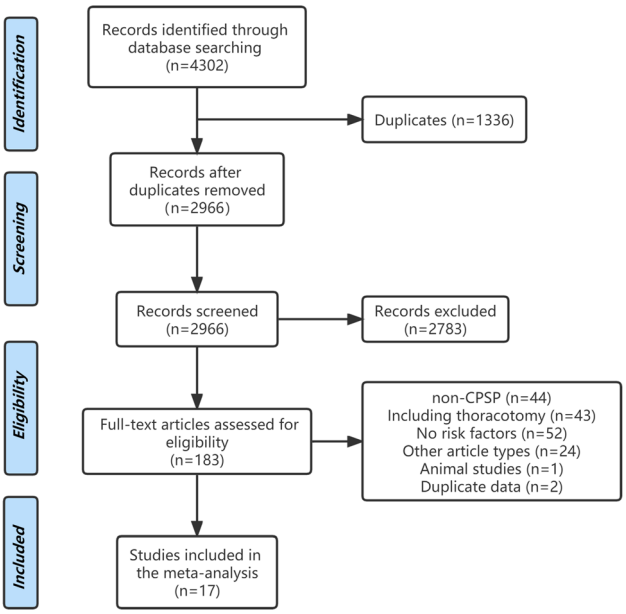

Fig. 1 Flow diagram of identified and selected studies

information on participants lost to follow-up. However, the selection of study populations, predictors, and measurement of outcome measures were reliable and valid. This suggested that the included studies had an acceptable risk of methodological bias.

Prevalence of CPSP After VATS

Based on the 17 included studies, the overall incidence rate of CPSP after VATS was 35.3% (95% CI 27.1–43.5%) when pooled using a random-effects model. The results indicated significant heterogeneity between the studies (I^2 = 99.13%). Given that discrepancies in the definition of CPSP may be a source of heterogeneity, we performed subgroup analyses of different pain scores. Pain scores > 3 were based on numerical rating scales, whereas pain scores > 1 indicated the presence of CPSP. Subgroup analysis showed a 41.0% (95% CI 34.6–47.3%) incidence rate of pain score ≥ 1 for CPSP after VATS, although only a 10.5% (95% CI 5.5–15.6%) incidence rate of pain score ≥ 3 after VATS. Figure 2 shows the results of the 17 studies that reported the occurrence of CPSP after VATS.

Predictors of CPSP After VATS

Qualitative Synthesis

Predictors of CPSP after VATS were confounded, and predictor estimates were contradictory; therefore, the predictors were categorized and pooled according to methodological quality and number of studies (Table 2).

All studies had 30 factors reported in the multivariate analysis at least once, of which 19 were independent factors with positive results. Female sex, age, and acute postsurgical pain (APSP) were identified as definite independent predictors of CPSP after VATS. In addition, there were four predictors with at least two high-quality studies revealing positive results; thus, they were classified as likely independent predictors of CPSP. These predictors were the number of ports, operation time, duration of drainage, and insufficient analgesia. Of the non-predictors, pathological stage was not considered an independent predictor of CPSP because two studies with a low risk of bias indicated negative results, and no study offered positive results. For the remaining predictors, no clear judgment could be made from the adjusted results owing to the small number or insufficient quality of the studies.

Table 1 Characteristics of the included studies

First author	Year	Country	Study design	Female/male	Age (years, CPSP vs. non-CPSP)	Sample size	Diagnosis	Outcome measure	Follow-up (months)	Covariate-adjusted risk factors
Yingying Zhang	2022	China	Retrospective	1250/1098	NA	2348	NA	NRS	3	Age, female sex, educational level less than junior school, preoperative pain, consumption of rescue analgesia postoperatively, consumption of sedative hypnotic postoperatively, wound infection
Susie Yoon	2021	Korea	Retrospective	1077/1145	53–71	2222	Lung cancer	NRS	36	Age, female sex, BMI, pathological stage, operation time, operation type, intercostal nerve blockade, postoperative radiotherapy, postoperative chemotherapy, year of surgery
Hong Zhao	2021	China	Retrospective	89/59	45–64	148	Lung nodules	BPI	3	Female sex, sufentanil dose during surgery, acute postoperative pain, consumption of rescue analgesia postoperatively

Table 1 continued

First author	Year	Country	Study design	Female/male	Age (years, CPSP vs. non-CPSP)	Sample size	Diagnosis	Outcome measure	Follow-up (months)	Covariate-adjusted risk factors
Maria Cattoni	2021	Italy	Retrospective	182/738	18–27	920	Primary spontaneous pneumothorax	NRS	2	Operation type, chest tube size, duration of drainage
Michael Semyonov	2021	Israel	Retrospective	53/38	NA	91	Mix	VAS	6	Female sex, ethnicity, operation type
Jianrong Hu	2021	China	Retrospective	138/83	54.49 ± 10.37 56.88 ± 12.23	221	Mix	NRS	3	Female sex, acute postoperative pain, postoperative analgesia
Xia Ji	2021	China	Retrospective	27/23	NA	50	Lung cancer	VAS	2	Female sex, duration of drainage, postoperative analgesia
Jie Wang	2021	China	Retrospective	38/130	13.4 ± 4.7 10.9 ± 3.9	168	Funnel chest	VAS	3	Age, weight, severity, preoperative complications, postoperative complications, acute postoperative pain
Yao Tong	2020	China	Retrospective	1905/1167	56.8 ± 11.7	3072	Lung cancer	NRS	3	Female sex, smoking history, operation time, port number, duration of drainage, acute postoperative pain
Yiyang Feng	2020	China	Prospective	86/106	50.9 ± 8.7 61.7 ± 6.0	192	Lung cancer	NRS	2	Age, female sex, acute postoperative pain, duration of drainage

Table 1 continued

First author	Year	Country	Study design	Female/male	Age (years, CPSP vs. non-CPSP)	Sample size	Diagnosis	Outcome measure	Follow-up (months)	Covariate-adjusted risk factors
Xianfei Yan	2019	China	Prospective	83/67	28–74	150	Lung cancer	VAS	≥ 5	Age, female sex, duration of drainage, postoperative analgesia
Caiwei Li	2018	China	Retrospective	107/125	61.21 ± 10.51	232	Lung cancer	NRS	6	Operation time, acute postoperative pain, port number, tumor location, pathological stage
Qingzhen Xu	2017	China	Retrospective	58/141	NA	199	Mix	SF-MPQ	3	Age, acute postoperative pain
Jianning Lan	2017	China	Retrospective	94/63	55.0 ± 9.2 54.8 ± 10.6	157	Lung cancer	NRS	3	Duration of drainage, postoperative chemotherapy, smoking history, ASA classification
Qiaoyan Zhao	2016	China	Retrospective	83/81	53.1 ± 10.4 55.4 ± 9.3	164	Mix	NRS	3	Female sex, acute postoperative pain, postoperative analgesia
Xiaolin Ji	2014	China	Prospective	48/48	56.50 (IQR 22–76) 64 (IQR 26–78)	96	Mix	VAS	3	Cold pain threshold
Hui Wang	2014	China	Retrospective	45/50	53.60 ± 13.10	95	Mix	NRS	3	Female sex, acute postoperative pain

ASA American Society of Anesthesiologists, *BMI* body mass index, *BPI* Brief pain inventory, *IQR* interquartile range, *NA* not applicable, *NRS* numerical rating scale, *SF-MPQ* Short-form of McGill Pain Questionnaire, *VAS* visual analog scale

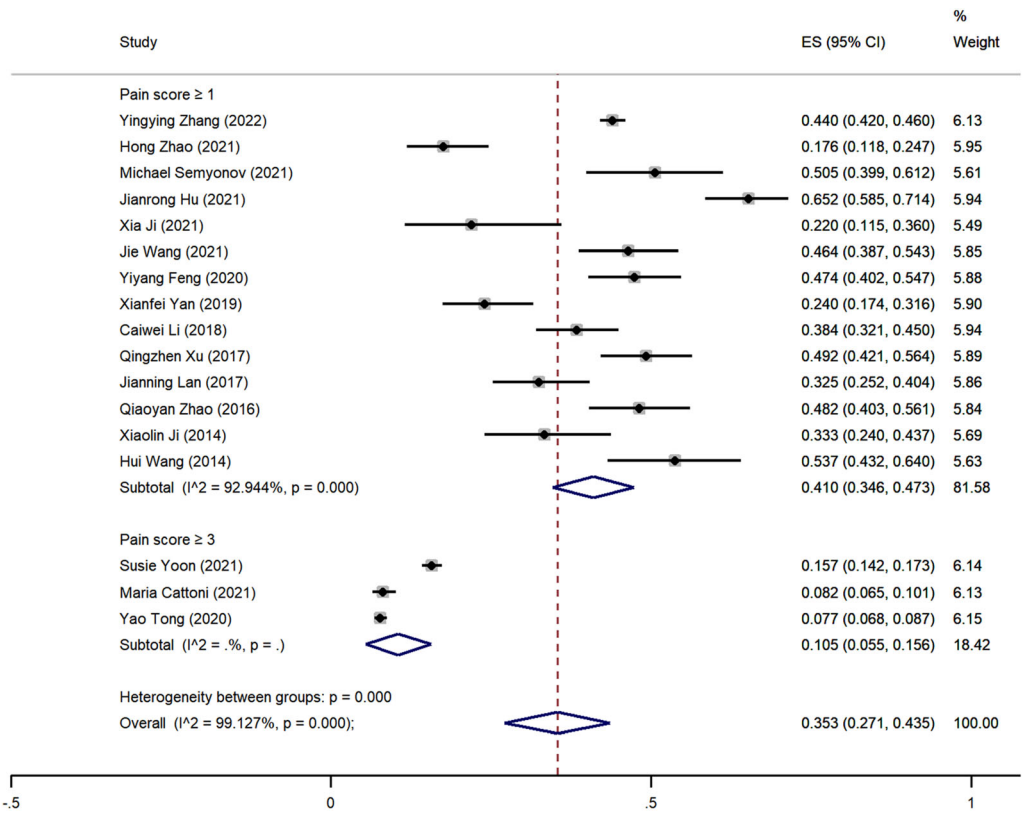

Fig. 2 Results of the subgroup analyses of the prevalence of chronic postsurgical pain after video-assisted thoracoscopic surgery. *ES* effect size, *CI* confidence interval

Quantitative Synthesis

We performed a meta-analysis of predictors evaluated in two or more studies. The unadjusted OR (uOR) was merged with the adjusted OR (aOR) to make the estimates of each predictor more thorough [18], as this permits the inclusion of studies with negative outcomes. Continuous variables from the baseline data were pooled to determine the predictive effect of these factors.

Female Sex

The association of female sex with the occurrence of CPSP was investigated in 17 studies that included 10,525 patients who underwent VATS. Six uORs were employed to supersede absent values because of their nonsignificance. Owing to the high heterogeneity between studies (I^2 = 84.2%), the 17 studies were pooled using a random-effects model. The results revealed that female patients who underwent VATS had a significantly higher risk of CPSP than that of male patients (OR 1.58; 95% CI 1.20–1.96) (Fig. 3I).

Advanced Age

Nine studies were included in the analysis of the influence of age on the occurrence of CPSP after VATS, including six multivariate analyses and three univariate analyses. The combined effects showed that older patients had a lower risk of CPSP after VATS than younger patients (OR 0.92; 95% CI 0.85–0.99) (Fig. 3II). A meta-analysis of continuous variables across the eight studies revealed that younger patients were more likely to develop CPSP after VATS (SMD = − 0.16; 95% CI − 0.24 to 0.07) (Fig. 3III). Random-effects models were used to pool the effects because of considerable heterogeneity between studies (I^2 = 76.4% and 92.5%, respectively).

Table 2 Estimates of the association between unique predictors and chronic postsurgical pain

Unique predictors	NOS ≥ 7		NOS < 7		Qualitative synthesis
	S	NS	S	NS	
Female sex	6	2	3	0	Definite
Age	4	2	0	0	Definite
Acute postoperative pain	7	0	1	0	Definite
Duration of drainage	2	1	2	1	Likely
insufficient analgesia	2	1	1	0	Likely
Operation time	2	0	1	0	Likely
Port number	2	0	0	0	Likely
Pathological stage	0	2	0	0	Not a predictor
Educational level less than junior school	1	0	0	0	Unclear
Preoperative pain	1	0	0	0	Unclear
Induction of rescue analgesia postoperatively	1	1	0	0	Unclear
Administration of sedative–hypnotic postoperatively	1	0	0	0	Unclear
Wound infection	1	0	0	0	Unclear
Operation type	0	1	1	1	Unclear
Severity	1	0	0	0	Unclear
Postoperative complications	1	0	0	0	Unclear
Cold pain threshold	1	0	0	0	Unclear
Postoperative chemotherapy	1	1	0	0	Unclear
BMI	0	1	1	0	Unclear
Ethnicity	0	0	1	0	Unclear
Weight	0	1	0	0	Unclear
ASA classification	0	0	1	0	Unclear
Intercostal nerve blockade	0	1	0	0	Unclear
Postoperative radiotherapy	0	1	0	0	Unclear
Year of surgery	0	1	0	0	Unclear
Sufentanil dose during surgery	0	1	0	0	Unclear
Chest tube size	0	0	0	1	Unclear
Preoperative complications	0	1	0	0	Unclear
Smoking history	0	1	0	1	Unclear
Tumor location	0	1	0	0	Unclear

ASA American Society of Anesthesiologists, *BMI* body mass index, *NOS* Newcastle–Ottawa Scale, *NS* nonsignificance, *S* significance

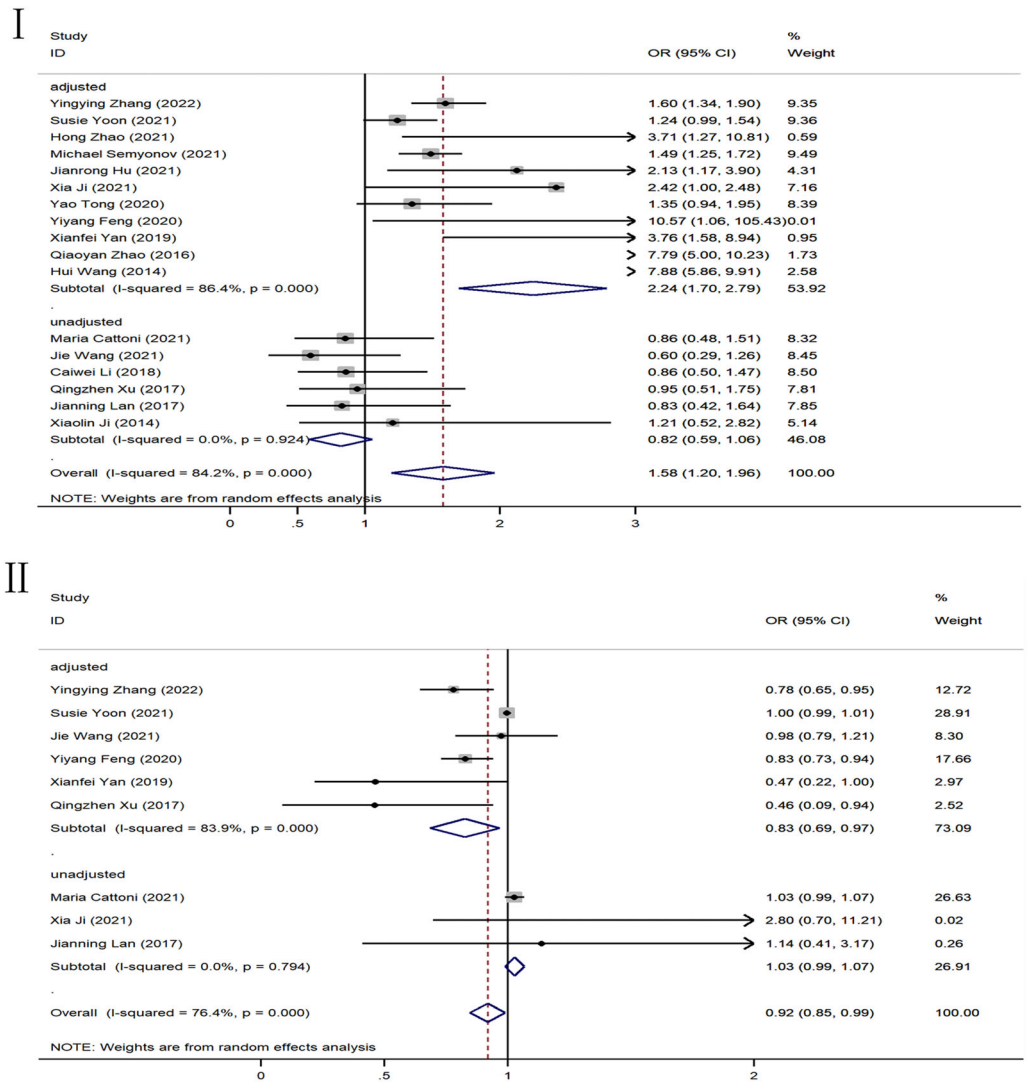

Fig. 3 Forest plot of predictors of chronic postoperative pain after video-assisted thoracoscopic surgery. **I** Female sex, **II** OR used as the effect estimate of age, **III** SMD used as the effect estimate of age. *CI* confidence interval, *OR* odds ratio, *SMD* standardized mean difference

Acute Postsurgical Pain

Nine multifactorial studies indicated an association between APSP and CPSP events after VATS. Our analysis indicated that patients with APSP after VATS were more likely to develop CPSP than their counterparts (OR 1.84; 95% CI 1.57–2.12) (Fig. 4I). Moreover, a pooled analysis of APSP scores based on patient characteristic data revealed that patients with CPSP had higher APSP scores than their counterparts (SMD 0.67; 95% CI 0.08–1.26) (Fig. 4II). Owing to the small heterogeneity between the aforementioned studies (I^2 = 49.1% and 0%), a fixed-effects model was utilized to assess their pooled effects.

Postoperative Analgesia

The aORs of five studies and the uORs of one study were pooled to estimate the effect of postoperative analgesia on the development of CPSP after VATS. A random-effects model was used to assess the results because of the notable heterogeneity between studies (I^2 = 88.0%). The pooled results showed that

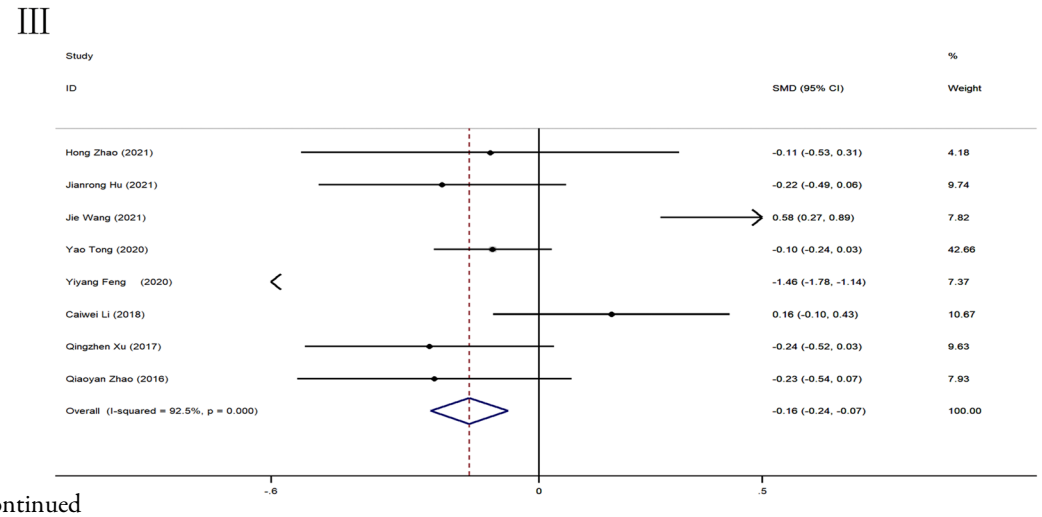

Fig. 3 continued

postoperative analgesia significantly reduced the risk of CPSP after VATS (OR 0.54; 95% CI 0.17–0.91) (Fig. 4III).

Port Number

Multivariate analysis of two studies examined the effect of port number on CPSP after VATS. There was insignificant heterogeneity between the studies (I^2 = 30.4%); therefore, a fixed-effects model was used to assess the pooled results. The analysis revealed that three-port thoracoscopic surgery increased the risk of CPSP (OR 4.32; 95% CI 3.51–5.13) (Fig. 4IV).

Operative Time

The aORs of three multivariate analyses were combined to determine whether the operative time was a predictor of CPSP after VATS. On the basis of the slight heterogeneity between studies (I^2 = 40.5%), a fixed-effects model was used and revealed that the risk of CPSP increased with a prolonged operation time (OR 1.007; 95% CI 1.003–10.010) (Fig. 5I). However, the results of the random-effects model for a continuous variable with significant heterogeneity (I^2 = 76.8%) indicated that the difference in operative time between the CPSP and non-CPSP groups was not statistically significant (SMD 0.13; 95% CI − 0.04 to 0.29) (Fig. 5II).

Duration of Drainage

Six studies evaluated drainage duration as a predictor using multivariate analysis. The results of the meta-analysis showed that a longer duration of postoperative drainage increased the risk of CPSP after VATS (OR 1.08; 95% CI 1.05–1.12) (Fig. 5III). This resulted from fixed-effects model pooling based on the low heterogeneity (I^2 = 34.1%). However, analysis derived from baseline data showed no significant difference between the CPSP and non-CPSP groups regarding drainage time (SMD 0.15; 95% CI − 0.25 to 0.55) (Fig. 5IV). This was based on the results of a random-effects model owing to the apparent heterogeneity (I^2 = 93.7%).

Postoperative Chemotherapy

After one missing variable was added that was nonsignificant in the univariate analysis, three studies involving the effect of postoperative chemotherapy on the occurrence of CPSP after VATS were included in the meta-analysis. Our analysis showed that postoperative chemotherapy significantly increased the risk of CPSP occurrence after VATS (OR 1.58; 95% CI 1.07–2.09) (Fig. 6I). No heterogeneity existed between the studies (I^2 = 0.0%); thus, a fixed-effects model was employed to evaluate the pooled results.

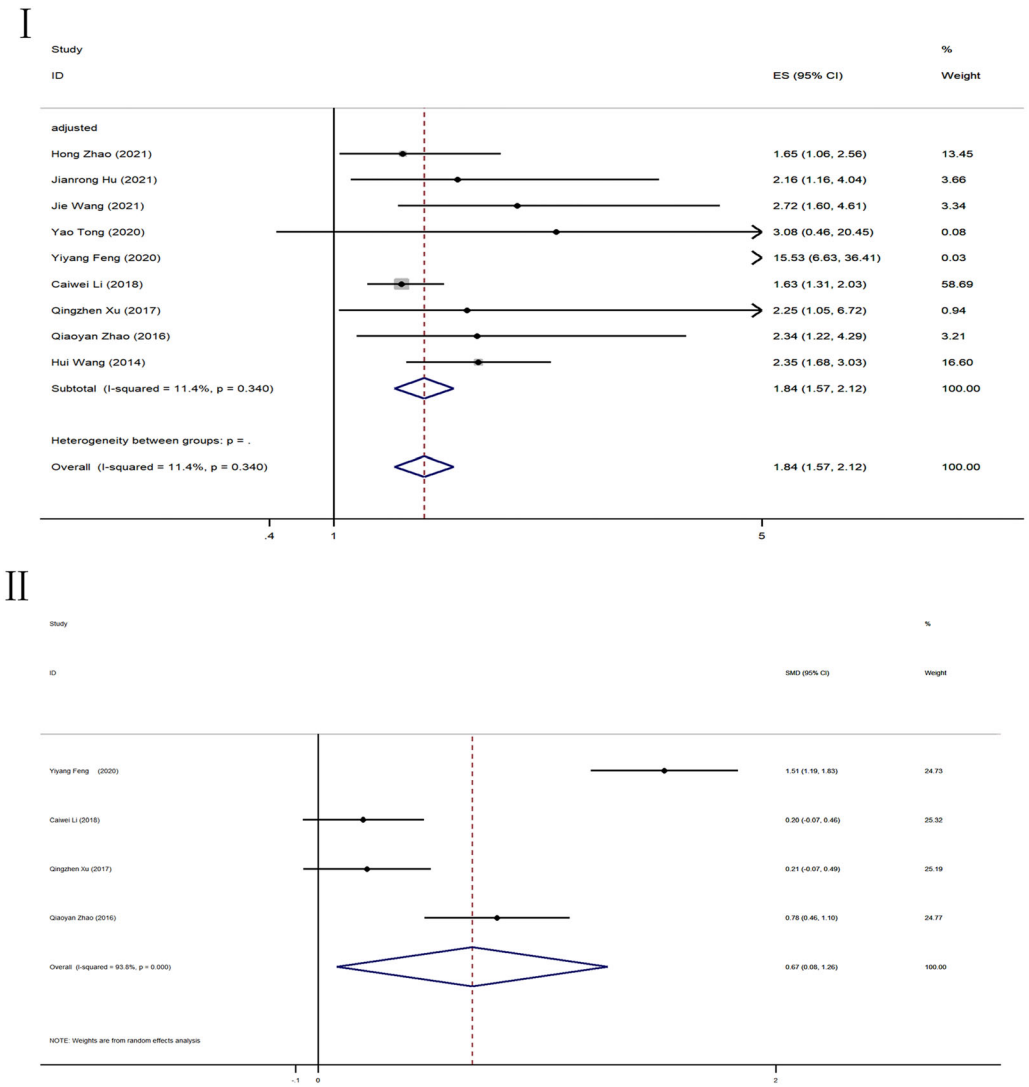

Fig. 4 Forest plot of predictors of chronic postoperative pain after video-assisted thoracoscopic surgery. **I** OR used as the effect estimate of acute postoperative pain, and **II** SMD used as the effect estimate of acute postoperative pain, **III** postoperative analgesia, **IV** OR used as the effect estimate of operative time. *CI* confidence interval, *OR* odds ratio, *SMD* standardized mean difference

Educational Level Less Than Junior School

Only three studies evaluated the effect of educational level on the occurrence of CPSP after VATS. The included studies had low heterogeneity (I^2 = 0%), and a fixed-effects model was used to evaluate the results. The pooled effect showed that an educational level less than junior school was more likely to lead to CPSP (OR 1.27; 95% CI 1.05–1.48) (Fig. 6II).

Smoking and Drinking Histories

Our meta-analysis results showed that patients undergoing VATS with smoking or drinking histories had a lower risk of CPSP than their counterparts (OR 0.80; 95% CI 0.65–0.95 and OR 0.77; 95% CI 0.60–0.94, respectively) (Fig. 6III, IV). Although the analysis was based on a fixed-effects model because the heterogeneity between the studies was low (I^2 = 19.2%; I^2 = 0.0%), the results should be

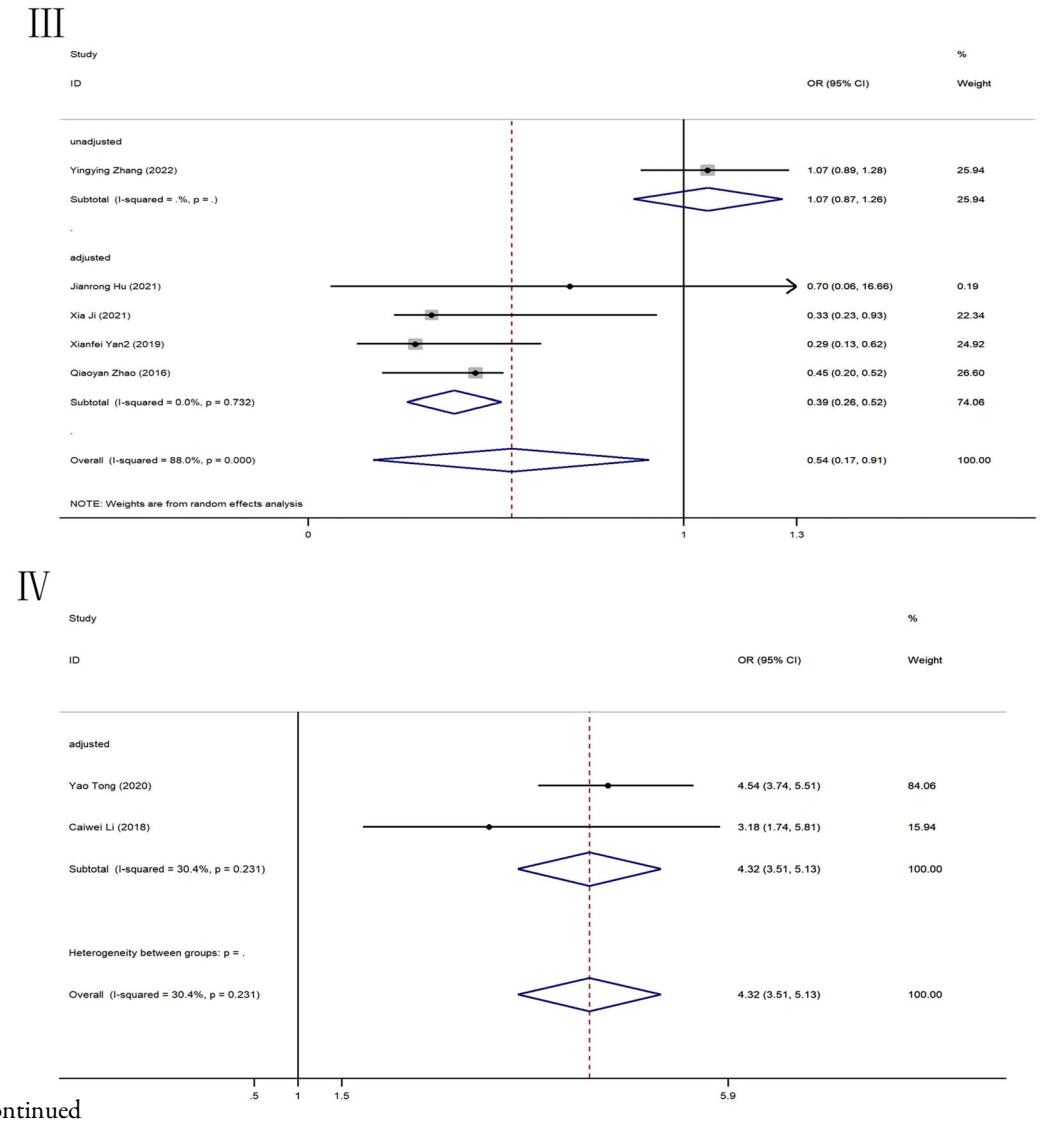

Fig. 4 continued

interpreted with caution because they did not adjust for the effect of sex.

Negative Results

Postoperative rescue analgesic use, American Society of Anesthesiologists grade, body mass index, weight, tumor nature and stage, intraoperative fentanyl and remifentanil use, intraoperative nerve block use, blood loss, hypertension, and diabetes mellitus showed negative results in this meta-analysis (see Figs. S1–S10 in the electronic Supplementary Material). On the basis of the pooled effects, these factors were not associated with the occurrence of CPSP after VATS.

Publication Bias and Sensitivity Analysis

In our meta-analysis, funnel plots showed publication bias for three factors: female sex, age, and APSP. The results revealed incomplete symmetry between the left and right sides of the funnel plot, suggesting the existence of some publication bias (see Fig. S11 in the electronic Supplementary Material). Nevertheless, quantification using Egger's linear regression revealed no significant bias for female sex ($P = 0.92$), age ($P = 0.25$), and APSP ($P = 0.11$)

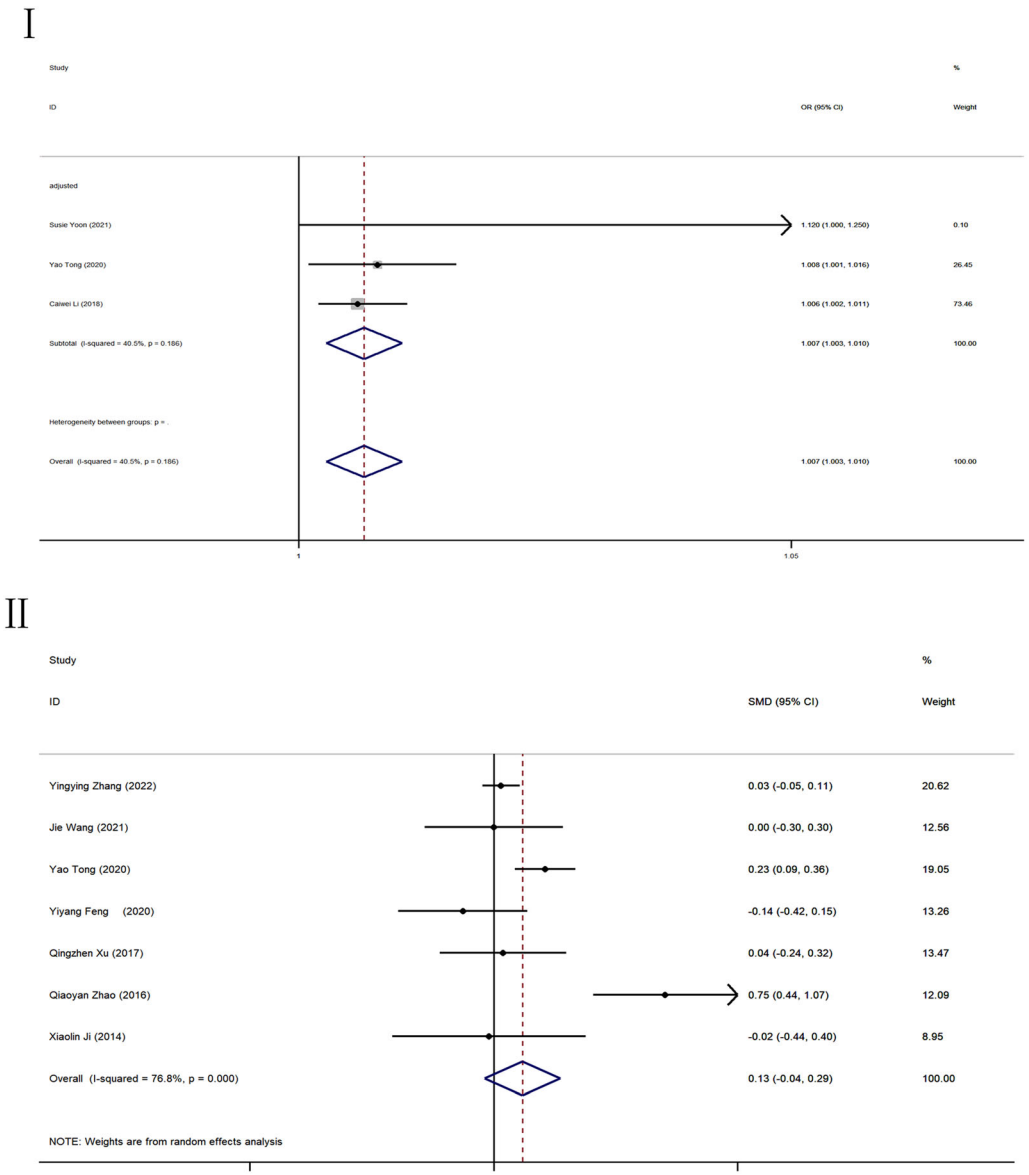

Fig. 5 Forest plot of predictors of chronic postoperative pain after video-assisted thoracoscopic surgery. **I** SMD used as the effect estimate of operative time, **II** port number, **III** OR used as the effect estimate of duration of drainage, and **IV** SMD used as the effect estimate of duration of drainage. *CI* confidence interval, *OR* odds ratio, *SMD* standardized mean difference

(see Fig. S12 in the electronic Supplementary Material). Furthermore, the effect of publication bias on the stability of the results was detected using the trim-and-fill method. After the trim-and-fill analysis, the results did not change; therefore, the pooled results were considered robust (see Fig. S13 in the electronic Supplementary Material). This study also performed a sensitivity analysis of the defined predictors of CPSP after VATS. The sensitivity analysis indicated that the meta-analysis results for each exposure factor were consistent with low sensitivity, suggesting that the results of

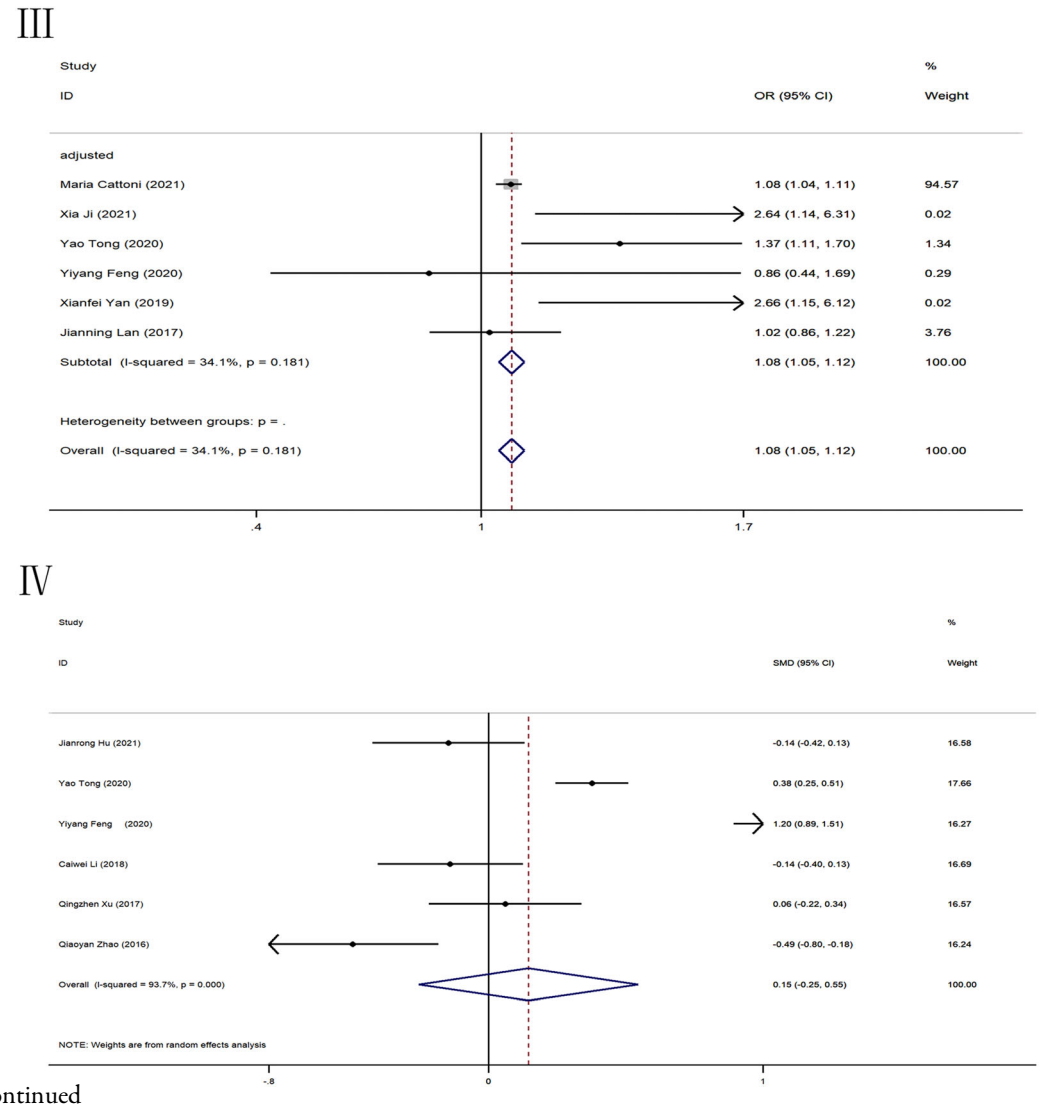

Fig. 5 continued

this study were stable and reliable (Fig. S14 in the electronic Supplementary Material).

DISCUSSION

To our knowledge, this is the first systematic review of the prevalence and predictors of CPSP after VATS. The primary outcome of this study demonstrated a prevalence of CPSP after VATS of 35.3% and identified three definite CPSP predictors (female sex, age, and APSP) and four likely predictors (insufficient analgesia, operation time, port number, and duration of drainage) with qualitative and quantitative synthesis. Secondary outcomes showed that only by quantitative analysis, postoperative chemotherapy and an educational level less than junior school were CPSP predictors after VATS. However, the results of smoking and drinking histories, which showed a reduced risk of CPSP, should be considered with caution. The effect of other potential predictors on the occurrence of CPSP after VATS requires further investigation. Furthermore, on the basis of the results of this study, pathological stage was not considered a predictor of CPSP. Despite robust results, additional large-scale studies are required as a few included studies only

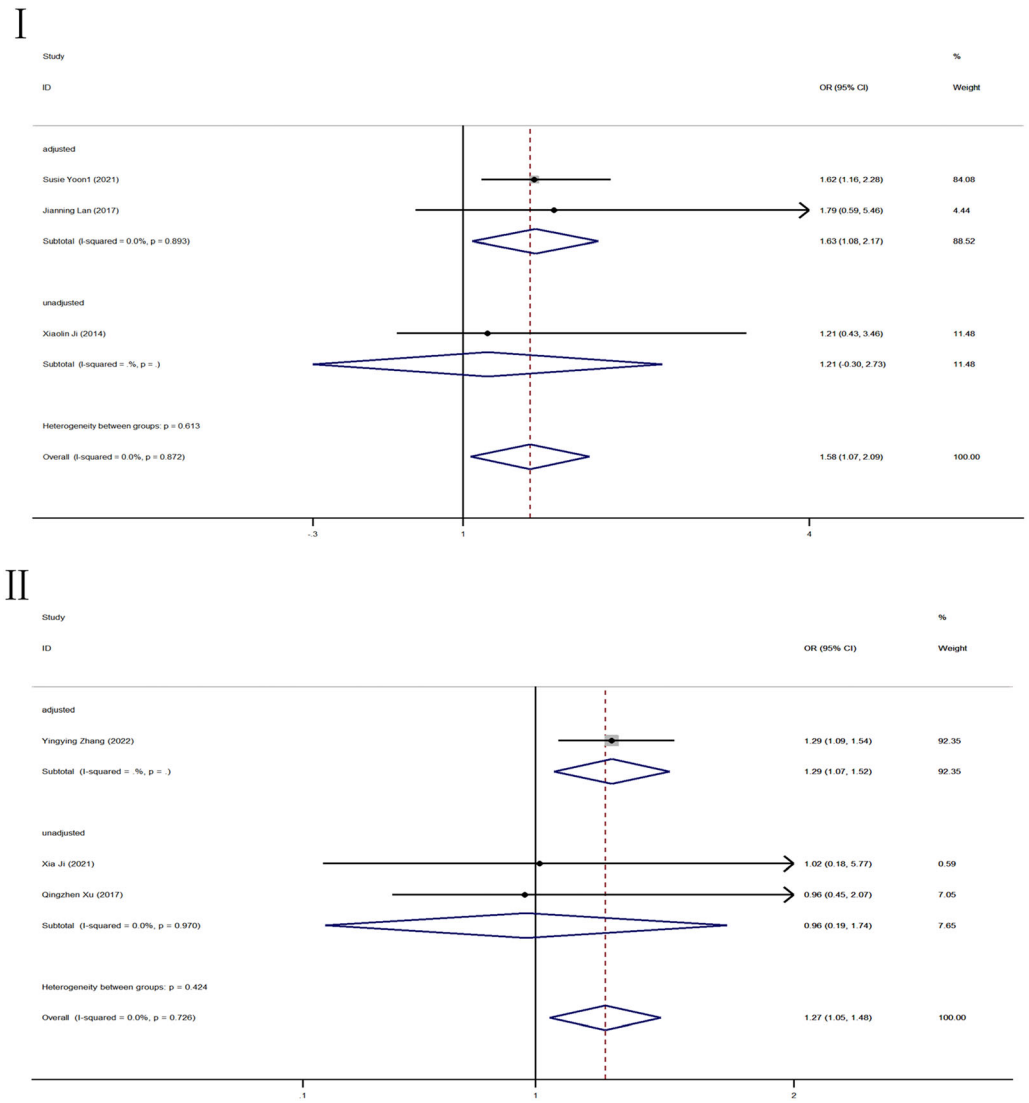

Fig. 6 Forest plot of predictors of chronic postoperative pain after video-assisted thoracoscopic surgery. **I** Postoperative chemotherapy, **II** educational level less than junior school, **III** smoking history, and **IV** drinking history. *95% CI* 95% confidence interval, *OR* odds ratio

considered certain predictors and the effect evaluation of some predictors has certain heterogeneity.

CPSP refers to chronic pain that develops or increases in intensity after surgery [6]. Owing to different patient characteristics, surgical types, and follow-up periods, the incidence rate of CPSP varies widely, ranging from 25% to 75% [3, 35]. One systematic study reported an overall incidence rate of 57% for CPSP after thoracotomy [36]. The incidence rate of CPSP is significantly lower following VATS than following thoracotomy. However, our meta-analysis revealed that the overall incidence rate of CPSP after VATS was 35.3%, with the incidence rates of CPSP with pain scores ≥ 3 and ≥ 1 being only 10.5% and as high as 41.0%, respectively. According to previous studies, any intensity of CPSP can decrease postoperative quality of life [3, 37]. Hence, a pain score of ≥ 1 should be considered clinically meaningful. On the basis of our current analysis, to raise clinicians' vigilance of CPSP, a pain score of 1–2 points should

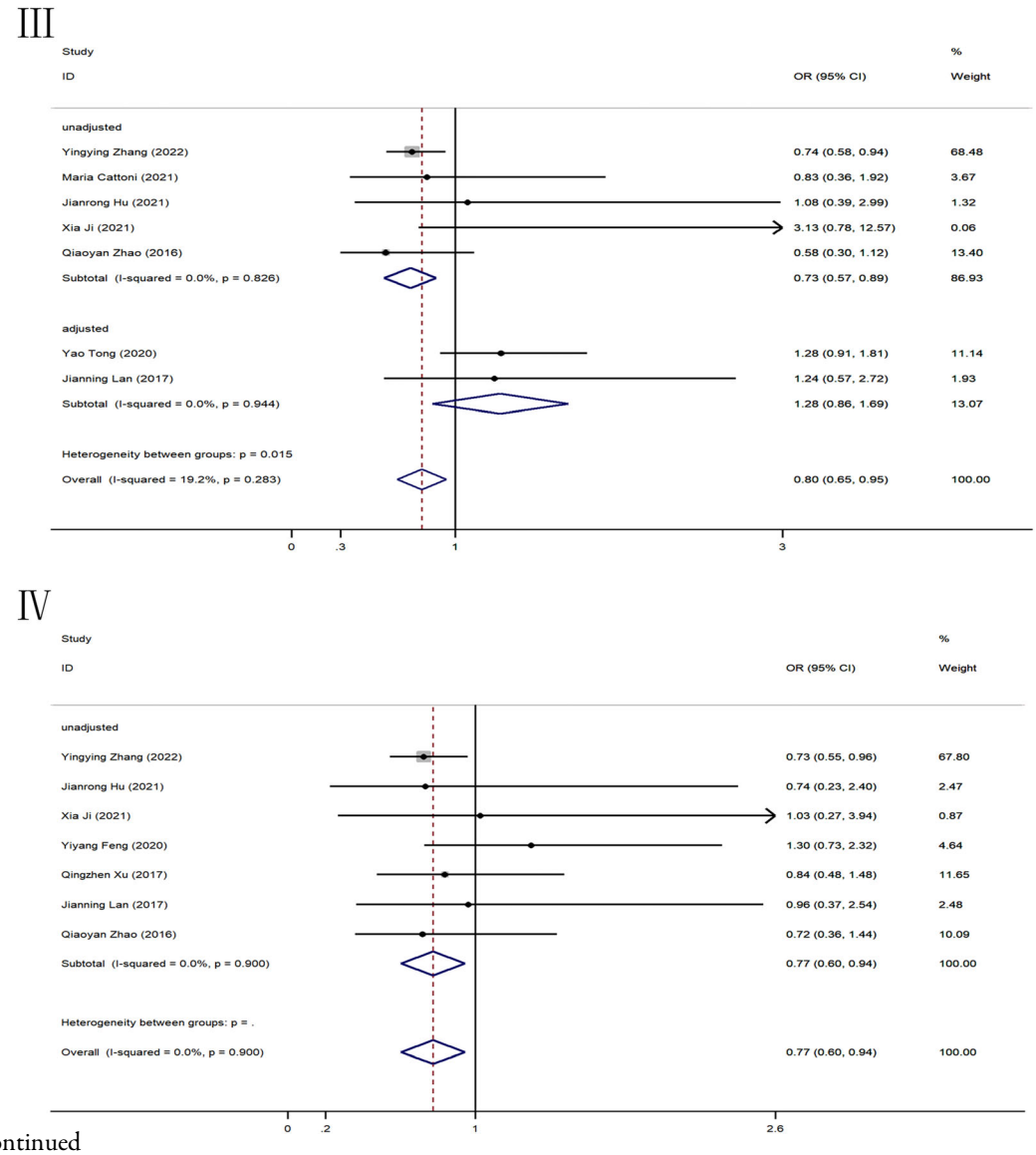

Fig. 6 continued

be reviewed to avoid neglecting patients with mild CPSP.

We performed subgroup analyses with different pain scores. Although the pooled results for CPSP incidence showed a decrease in heterogeneity, the group with scores ≥ 1 remained relatively heterogeneous. Going back to the original study, this may be due to differences in the duration of follow-up, type of disease, and underlying patient conditions. However, there are few related homogeneity studies, so we cannot conduct a meta-analysis. Therefore, further large-scale homogeneity studies are needed to confirm our results.

Women have an increased risk of sensitivity and clinical pain [38]. Similarly, this study demonstrated an increased risk of CPSP in female patients after VATS, even with the addition of select values that were discarded owing to nonsignificance. However, the precise reason that chronic pain is more common in women than in men is not fully understood. Studies have established that women have lower pain thresholds and tolerance and are more likely to experience additional intense

pain and less pleasant sensations than men [39]. This phenomenon may be due to sex differences in the drivers of neuroimmune interactions in the development and maintenance of pain hypersensitivity and chronic pain [40]. Furthermore, several psychosocial mechanisms are involved in biological mechanisms, including differences in pain management strategies, discrepancies in sociocultural beliefs, and women's greater early exposure to environmental stress [40].

Notably, our meta-analysis showed that patients undergoing VATS with smoking and drinking histories had a lower risk of developing CPSP. This may be due to sex-related differences in smoking and drinking histories, and we could not adjust for sex. Most studies did not determine a direct association between drinking history and CPSP [11, 41]; however, patients with a smoking history had an increased incidence of CPSP [42]. Substances in tobacco increase the body's inflammatory response and oxidative stress and can lead to increased pain sensitivity by remodeling neural circuits [42]. Taken together, our results should be cautiously considered.

Age is a crucial factor in the occurrence of CPSP; the younger the age, the higher the risk of CPSP [37, 43]. This study showed that the patients' mean age was lower in the CPSP group than in the non-CPSP group. A further meta-analysis of aOR and uOR revealed that advanced age was a protective factor for CPSP in patients who underwent VATS. This phenomenon may be related to increased pain thresholds due to aging and decreased pain perception, organ dysfunction, and other conditions that can seriously affect chronic pain perception and response [44]. Moreover, older people are more stoic regarding pain and more reluctant to report pain when it occurs than younger people are [45]. Conversely, lower educational levels lead to pain catastrophizing [46]. This socioeconomic characteristic plays a vital role in pain perception. Our study also showed that an educational level below junior high school level is more likely to predispose patients to CPSP. Thus, physicians should pay particular attention to counseling such patients prior to and during treatment.

Our study also discovered that several surgical and therapeutic factors were related to the occurrence of CPSP after VATS. Some studies have suggested that prolonged operation time increases the risk of CPSP [47]. Although minimally invasive, VATS can increase the incidence of CPSP if the operative time is prolonged. Furthermore, three-port VATS, increased drainage time, and administration of postoperative chemotherapy also contributed to the increased incidence of CPSP. The underlying mechanisms may be related to intercostal nerve injury [48]. Tissue edema caused by postoperative chemotherapy can also have an effect similar to that noted in double crush syndrome [49]. Moreover, postoperative chemotherapy leads to central sensitization, contributing to spontaneous pain and hyperalgesia [50]. Therefore, surgical and perioperative management plans should be optimized, patients who need postoperative chemotherapy should be carefully monitored, and pain management should be instituted as early as possible.

Regarding perioperative pain-related parameters, our study ascertained that APSP was a risk factor for CPSP after VATS, whereas postoperative analgesia was a protective factor. A current study showed that CPSP can transition from APSP [4]; however, it is not just a simple continuation of acute pain [51]. It may involve structural remodeling and reorganization of synapses, cells, and circuits, which contribute to the chronicity of pain [52]. Intraoperative tissue damage plays a decisive role in CPSP development and triggers profound modifications in peripheral and central sensory circuits. Once these structural changes occur, it is too late to effectively intervene; therefore, preventing acute pain from progressing to chronic pain is a top priority. Our study also confirmed that postoperative analgesia can reduce the risk of CPSP after VATS. Consequently, clinicians should be aware of the importance of pain management during the acute phase after VATS. However, currently available drugs and regimens for the effective treatment of acute pain remain limited, and there is an urgent need to develop new interventions to prevent the acute pain progression to CPSP.

This study had some limitations. First, the predictors in the included studies were sorted, resulting in few included studies and difficulty analyzing some predictors, thus limiting the reliability of our results regarding certain predictors. Second, as a result of the evolution of definitions, the definitions of CPSP varied slightly across studies [4, 34], which is bound to produce a certain degree of heterogeneity. Third, we combined the uOR from the baseline data of the study with the aOR from the multivariate analysis. Although this mitigated the inflated assessments of some predictors, it increased heterogeneity. Fourth, some factors that may have had collinearity (e.g., smoking and drinking histories) could not be adjusted for because we did not have access to the raw data of the included studies. Finally, since most of the existing studies on the risk factors of CPSP after VATS are retrospective, the number of prospective studies included in this study is limited, which will also affect our conclusion. Thus, although our results are robust, the results should be interpreted with caution owing to limited data.

CONCLUSION

This systematic review and meta-analysis of the incidence and risk factors for CPSP after VATS provides essential insights to guide future pain management after VATS. The high prevalence of CPSP after VATS should not be underestimated. Female sex, age, and APSP were definitive predictors of CPSP development following VATS. Moreover, several likely predictors were identified, including insufficient analgesia, operation time, port number, duration of drainage, postoperative chemotherapy, and educational level less than junior school. However, further large-scale investigations are required to confirm our results because of the inclusion of retrospective studies and unavoidable limitations in this systematic review and meta-analysis.

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Disclosures. Wei-can Chen, Yu-yan Bai, Li-hong Zhang, Yi-bin Liu, Chu-yun Liu, Jin-wei Liang, and He-fan He have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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