Original Article

A comparison of non-intubated video-assisted thoracic surgery with spontaneous ventilation and intubated video-assisted thoracic surgery: a meta-analysis based on 14 randomized controlled trials

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Background: Video-assisted thoracic surgery (VATS) generally involves endotracheal intubation under general anesthesia. However, inevitably, this may cause intubation-related complications and prolong the postoperative recovery process. Gradually, non-intubated video-assisted thoracic surgery (NIVATS) is increasingly being utilized. However, its safety and efficacy remain controversial.

Methods: Randomized controlled trials (RCTs) published up to August 2020 were selected from the Cochrane Library, Web of Science, PubMed, Embase, and ClinicalTrials.gov databases and included in this study according to the inclusion criteria. Two reviewers screened these RCTs and independently extracted the relevant data. After assessing the risk of bias in these RCTs, a meta-analysis was performed using Review Manager 5.3. Pooled data were meta-analyzed using a random-effects model.

Results: Meta-analysis data demonstrated that the mean difference (MD) in the length of hospital stay between non-intubated patients and intubated patients was –1.41 days, with a 95% confidence interval (CI) of –2.47 to –0.34 (P=0.01). The visual analogue scale (VAS) score between the two groups showed a MD of –0.34 (95% CI: –0.58 to –0.10; P=0.006). Patients who underwent NIVATS presented with lower rates of overall complications [odds ratio (OR) 0.41; 95% CI: 0.25 to 0.67; P=0.0004], air leak (OR 0.45; 95% CI: 0.24 to 0.87; P=0.02), pharyngeal discomfort (OR 0.08; 95% CI: 0.04 to 0.17; P<0.00001), hoarseness (OR 0.06; 95% CI: 0.02 to 0.21; P<0.00001), and gastrointestinal reactions (OR 0.23; 95% CI: 0.10 to 0.53; P=0.0005) compared to intubated patients. The anesthesia satisfaction scores in the NIVATS group were significantly higher than those of the VATS group (MD 0.50; 95% CI: 0.12 to 0.88; P=0.009). However, there were no statistically significant differences in the length of operation time (MD 0.90 hours; 95% CI: –0.23 to 2.03; P=0.12) and surgical field satisfaction (1 point) (OR 0.73; 95% CI: 0.34 to 1.59; P=0.43) between the two groups.

Conclusions: NIVATS is a safe and feasible form of intervention that can reduce the postoperative pain and complications of various systems and shorten hospital stay duration without prolonging the operation time.

Keywords: Thoracoscopic surgery; length of hospital stay; meta-analysis

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Introduction

At present, traditional endotracheal intubation with general anesthesia is a widely accepted method in thoracoscope surgery. Utilizing this procedure, patients receive one-lung ventilation, which provides a stable surgical field and operating space for the thoracoscope surgery (1). However, endotracheal intubation with general anesthesia is inevitably associated with a risk of complications such as airway hyperresponsiveness, postoperative sore throat, hoarseness, and pulmonary inflammatory reactions (2-4).

In recent years, the concept of "enhanced recovery after surgery" (ERAS) has been widely promoted, and non-intubated video-assisted thoracic surgery (NIVATS) has been increasingly used to avoid injury associated with tracheal intubation and the residual effects of muscle relaxants, thereby promoting the recovery of the patient's postoperative respiratory function and sputum discharge function, and reducing the occurrence of postoperative complications (5-8). This technique is currently being used in pleural effusion, spontaneous pneumothorax, empyema resection, wedge resection, lung volume reduction, thymectomy, segmentectomy, and lobectomy (9-12). However, complications such as intraoperative cough, mediastinal oscillation, hypercapnia, and hypoxemia remain unresolved and may require surgeons' more delicate and stable operation and improved anesthesia management. Also, laryngeal mask airway (LMA) inflation can cause a feeling of pharyngeal compression, and as a result, some patients may experience postoperative pharyngeal pain, pharyngeal nerve compression injury, and other deficiencies (13). Therefore, the implications of NIVATS are still not fully understood and remain controversial.

To date, there is a lack of a large sample, multi-center, and high-quality evidence to demonstrate the safety and efficacy of NIVATS and to determine whether it allows for an acceptable surgical field. Furthermore, it is unclear whether patients undergoing NIVATS experience shorter hospital stays and fewer postoperative complications such as pharyngeal discomfort and hoarseness. Therefore, in this study, operation time and surgical field satisfaction scores were used to evaluate the operation's safety from the surgeon's perspective. Short-term postoperative pain was measured by anesthesia satisfaction score and visual analogue scale (VAS) score (24 hours after surgery). The occurrence of complications evaluated postoperative rehabilitation quality, and the length of hospital stay was assessed to determine whether NIVATS was beneficial to the overall rehabilitation of patients. This information will be beneficial for the surgical decision-making process. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3039).

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were adopted for this investigation (14). This study is currently being registered with PROSPERO, and a registration number is pending. A systematic and comprehensive computer search was conducted using the Cochrane Library, Web of Science, PubMed, Embase, and ClinicalTrials.gov databases to screen for randomized controlled trials (RCTs) up to August 2020 by combining search terms such as "non-tracheal intubation", "non-intubated", "wake", "video-assisted thoracoscopic surgery", "VATS" and "thoracic disease". There were no restrictions on the year or country of publication. Also, manual filtering was performed on the list of references from the original articles and review articles to retrieve studies not detected in the database search.

Inclusion and exclusion criteria

Eligible studies were included according to the following criteria: (I) RCTs comparing non-intubated versus intubated general anesthesia in thoracic surgery; (II) the presences of sufficient data to conduct a study of mean differences (MDs) or odds ratio (OR); (III) both groups of patients in the study underwent thoracoscopic surgery; and (IV) the most recent study was selected in case of duplication. Exclusion criteria were as follows: (I) no comparison between non-intubation thoracoscopy and endotracheal intubation thoracoscopy; (II) intubated and non-intubate patients underwent different surgical procedures; (III) reviews, letters, editorials, expert opinions, case reports, and animal experiments, and (IV) a failure to extract relevant data from the study.

Data extraction

The authors used standard tables to extract data from the included studies independently. RCTs comparing the efficacy of NIVATS and video-assisted thoracoscopic surgery (VATS) in the treatment of thoracic diseases were

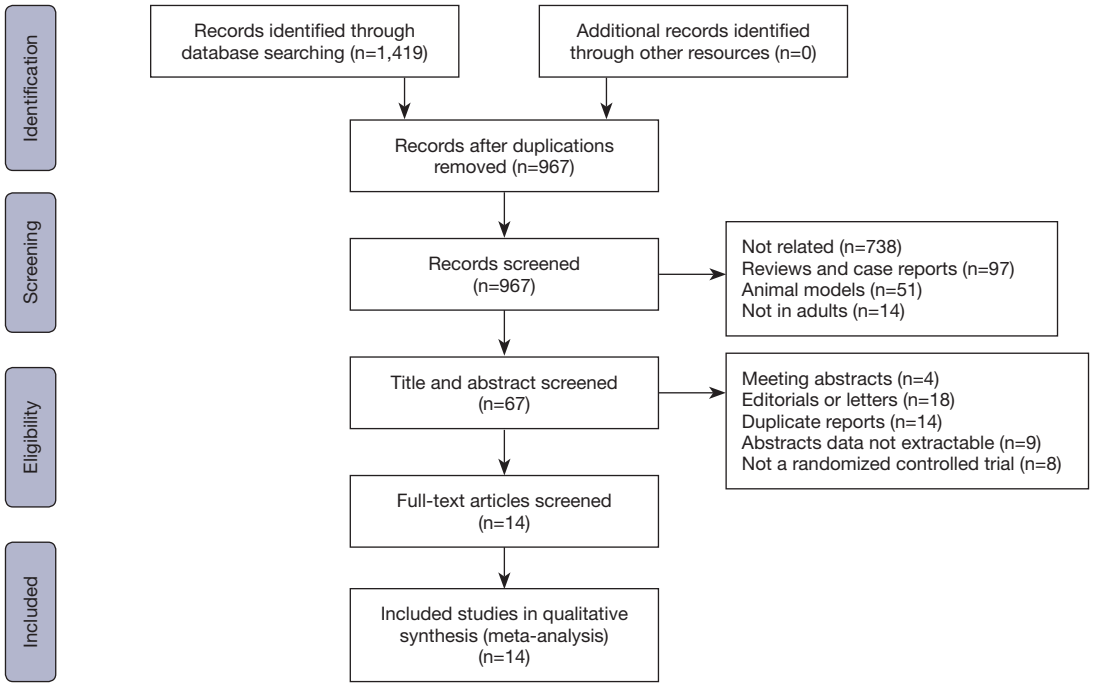

Figure 1 A flow diagram showing the selection process of the articles included in this meta-analysis.

searched. The two authors resolved any differences through discussion, and the corresponding author ultimately decided any disputes that could not be resolved.

Validity assessment

The Jadad scale was used to evaluate the quality of the selected publications, with a score of 3 or above defined as a high-quality study. The Cochrane collaboration bias risk assessment tools were used to evaluate the quality of the RCTs, and this involved the following seven aspects: (I) random sequence generation (selection bias); (II) allocation concealment (selection bias); (III) blinding of participants and personnel (performance bias); (IV) blinding of the outcome assessment (detection bias); (V) incomplete outcome data (attrition bias); (VI) selective reporting (reporting bias), and (VII) other bias. All aspects were evaluated according to "low bias", "unclear", and "high bias".

Statistical analysis

RevMan 5.3 software was used for meta-analysis, and the effect indicators were MD, 95% confidence interval (CI) for quantitative data, and OR and 95% CI: for qualitative data. Data were considered statistically significant when $P<0.05$. The heterogeneity of treatment effects between studies was measured using Higgins' inconsistency test (I^2). If $I^2 \leq 50\%$, the heterogeneity was accepted, and the fixed effects model was selected. If $I^2 > 50\%$, then heterogeneity was considered to be large. In this case, the source of heterogeneity was searched, and subgroup analysis, sensitivity analysis, or the random effects model was used for meta-analysis. The median and quartile range of continuous variables were converted to mean standard deviation using the sample mean estimation method (15) and the standard deviation estimation method (16) by using the online tool (http://www.comp.hkbu.edu.hk/~xwan/median2mean.html). Publication bias was evaluated by funnel plot test, Begg's test, and Egger's test.

Results

Search results

The basic characteristics of the included studies

A total of 14 RCTs were included in the study according to the PRISMA guidelines (shown in *Figure 1*), including 1,426 patients, with 707 patients in the non-intubated group and 719 patients in the intubated group (*Table 1*).

Table 1 Studies included in this meta-analysis

Study	Year	Country	Study design	Disease	Sample size (total/intervention/control)	Quality assessment (Jadad score)
Cai *et al.* (17)	2013	China	RCT	Pulmonary bulla	60/30/30	2
Chen *et al.* (18)	2016	China	RCT	Primary palmar hyperhidrosis	168/85/83	4
Hwang *et al.* (19)	2018	Korea	RCT	Spontaneous pneumothorax	41/21/20	3
Kocatürk *et al.* (20)	2019	Turkey	RCT	Variety	293/145/148	2
Liu *et al.* (21)	2015	China	RCT	Variety	347/167/180	3
Mao *et al.* (22)	2018	China	RCT	Pectus excavatum	60/30/30	3
Pompeo *et al.* (23)	2004	Italy	RCT	Pulmonary nodule	60/30/30	3
Pompeo *et al.* (24)	2007	Italy	RCT	Spontaneous pneumothorax	43/21/22	2
Pompeo *et al.* (25)	2012	Italy	RCT	Pulmonary emphysema	63/32/31	3
Pompeo *et al.* (26)	2013	Italy	RCT	Pleurodesis of malignant pleural effusion	40/20/20	2
Tacconi *et al.* (27)	2010	Italy	RCT	Variety	21/11/10	2
Vanni *et al*. (28)	2010	Italy	RCT	Variety	50/25/25	2
Wang *et al.* (29)	2014	China	RCT	Variety	100/50/50	3
Xiang *et al*. (30)	2020	China	RCT	Variety	80/40/40	3

RCT, randomized controlled trials.

As shown in *Table 1*, based on the Jadad scale, eight studies were of good quality (18,19,21-23,25,29,30) with scores of 3 or above. The types of surgery in these reports are mostly classified as thoracoscopic operations. Bullectomy (17,19,24), wedge resection (23), sympathectomy (18), talc pleurodesis (26), and pleural biopsy (20) are defined as minor thoracic surgery. Nuss surgery (22) and lung volume reduction surgery (25) are defined as moderate thoracic surgery. Lobectomy and segmentectomy (30) are defined as major thoracic surgery. The basic characteristics of the included studies are shown in *Table 1*.

Sensitivity analysis and bias risk assessment

Risk assessment of bias was conducted according to the bias risk assessment tool recommended by the Cochrane system. Most of the studies included in this paper described random methods, allocation concealment, blindness, and data integrity. There were nine studies (18,21-24,28-30) with a low risk of selection bias, using random numbers generated by the computer. A total of two studies (18,29) used the sealed envelope method, and four reports (22-24,28) used the opaque random sequence method. In terms of measurement bias, three studies (19,22,29) used the method of third-party measurement collection. However, some studies did not mention the bias risk assessment table, and the quality of the methodology was poor. The quality evaluation results of the included studies are shown in *Figure 2*.

Sensitivity analysis was performed by successively removing each of the included studies from the overall analysis. The results demonstrated that the other analyses' initial results were not altered except for postoperative air leakage, indicating that most of the results were stable (*Table 2*).

Meta-analysis results

Primary outcome

A total of eight articles (17,22-24,26-28,30) reported the length of hospital stay, but the heterogeneity was vast ($P<0.00001$, $I^2=97.0\%$). Subgroup analysis was conducted according to operation size, anesthesia mode, and ethnicity; however, each study's heterogeneity was still large (*Figures 3–6*). Sensitivity analysis showed that the MD deviated from the original 95% CI: after eliminating the study by Xiang *et al*. (30) (*Figure 7*), suggesting that this study

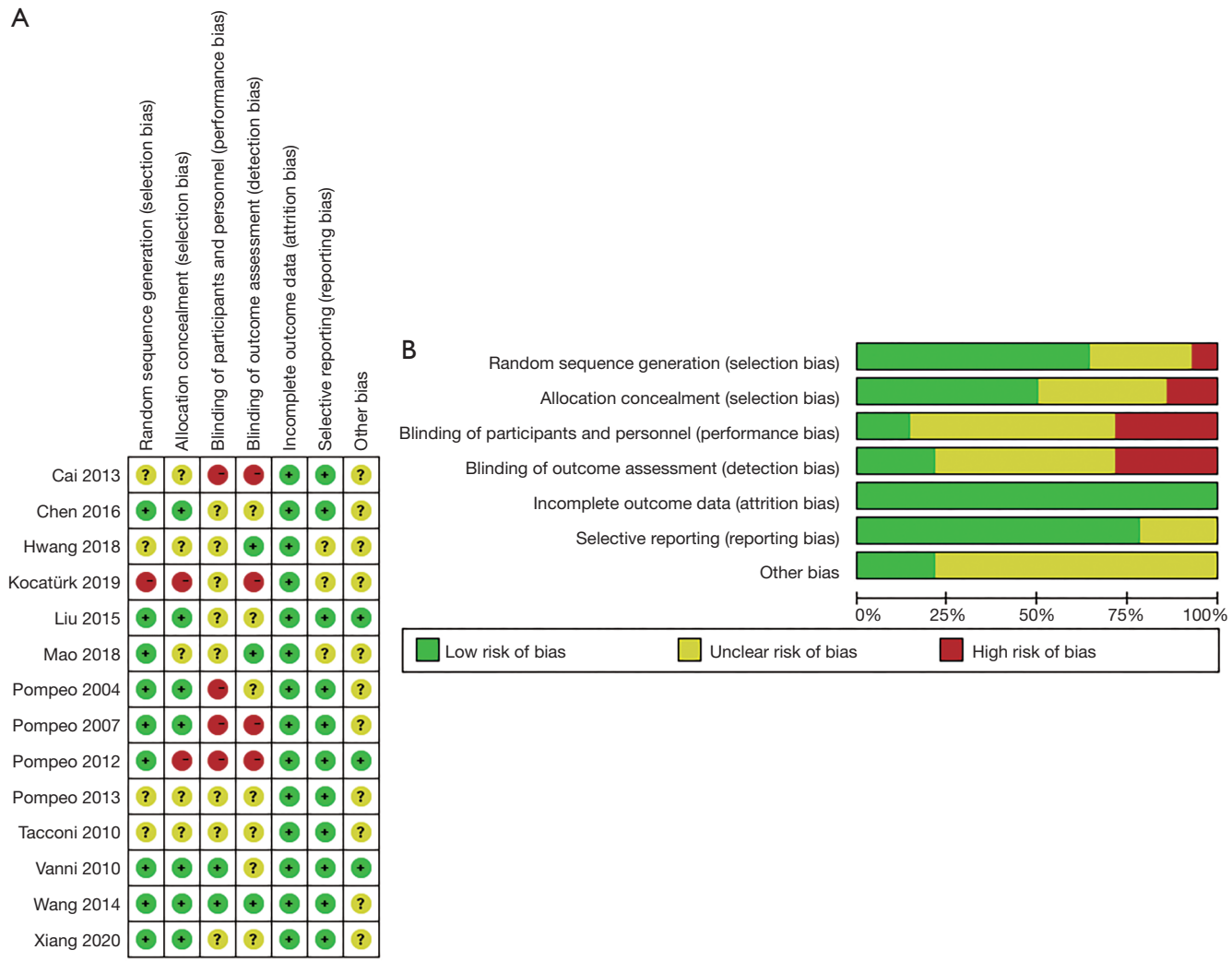

Figure 2 Risk of bias analysis for the RCTs. (A) Risk of bias summary reviewing the authors' judgments regarding each risk of bias item for each included study. (B) Risk of bias graph reviewing the authors' judgments regarding each risk of bias item presented as percentages across all included studies. RCTs, randomized controlled trials.

was the source of heterogeneity. The latter study's surgical methods included lobectomy and segmental lung resection, and the postoperative hospital stay was longer than that of other minor and moderate operations. The random effects model demonstrated that the length of hospital stay in the non-intubated group was significantly shorter compared to patients with intubation (MD –1.41; 95% CI: –2.47 to –0.34; P=0.01; *Figure 3*). The publication bias test was conducted, and both the Egger's and Begg's tests revealed no obvious publication bias (P=0.127 and P=0.902, respectively).

Secondary outcomes

Operation time

A total of 12 studies (17-20,22-24,26-30) reported the operation time, and the heterogeneity was large (P<0.0001, I^2 =81%). Sensitivity analysis showed that the heterogeneity was reduced to the acceptable range (P=0.36, I^2 =9%) after excluding the report by Kocatürk *et al.* (20). Unilateral and bilateral pleural biopsies were the main procedures examined in this study, explaining the significant difference in operation time. After exclusion, the remaining studies

Table 2 A sensitivity analysis comparison of patients in the NIVATS group and the VATS group

Outcomes	Studies, No.	NIVATS patients, No.	VATS patients, No.	MD/OR	95% CI	P	Study heterogeneity	
							I^2 (%)	P
Primary outcomes								
Hospital stay	8	207	207	−1.41	−2.47, −0.34	0.01	97	<0.00002
Secondary outcomes								
Operation time	12	363	360	0.90	−0.23, 2.04	0.12	9	0.36
Surgical field satisfaction	3	120	120	0.73	0.34, 1.59	0.43	0	0.88
Anesthesia satisfaction scores	4	82	82	0.50	0.12, 0.88	0.009	0	0.60
VAS scores	4	216	218	−0.34	−0.58, −0.10	0.006	0	0.53
Overall complications	8	481	496	0.41	0.25, 0.67	0.0004	0	0.76
Respiratory complications	8	481	496	0.37	0.21, 0.66	0.0006	0	0.93
Air leak	7	371	381	0.45	0.24, 0.87	0.02	0	0.87
Intubation-related complications	3	337	346	0.07	0.04, 0.16	<0.00001	0	0.95
Pharyngeal discomfort	4	185	183	0.08	0.04, 0.17	<0.00001	14	0.32
Hoarseness	3	100	100	0.06	0.02, 0.21	<0.00001	0	0.94
Gastrointestinal reactions	4	121	122	0.23	0.10, 0.53	0.0005	0	0.41
Postoperative atelectasis	3	203	215	0.33	0.06, 1.65	0.18	0	0.99
Pulmonary infection	4	384	399	0.40	0.13, 1.20	0.1	0	0.59

NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; MD, mean difference; OR, odds ratio; CI, confidence interval; VAS, visual analogue scale.

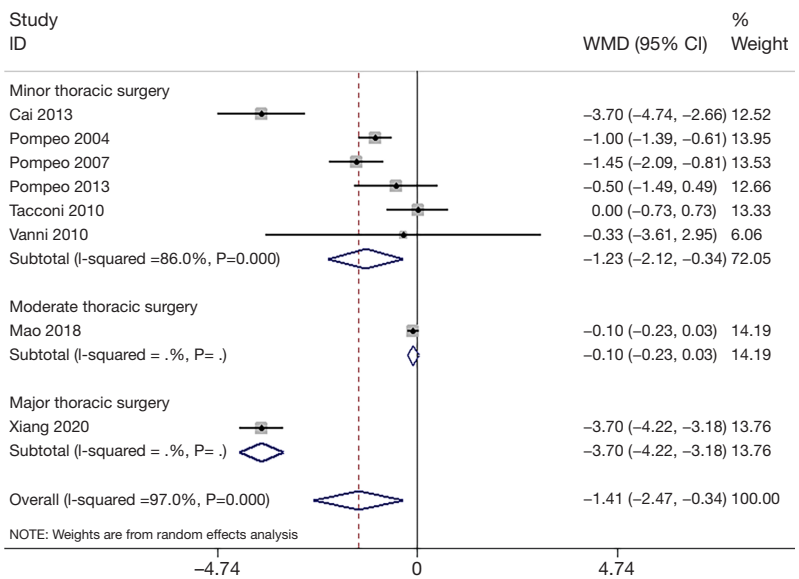

Figure 3 A forest plot showed the length of hospital stay for a subgroup analysis based on the size of the operation. WMD, weighted mean difference; CI, confidence interval.

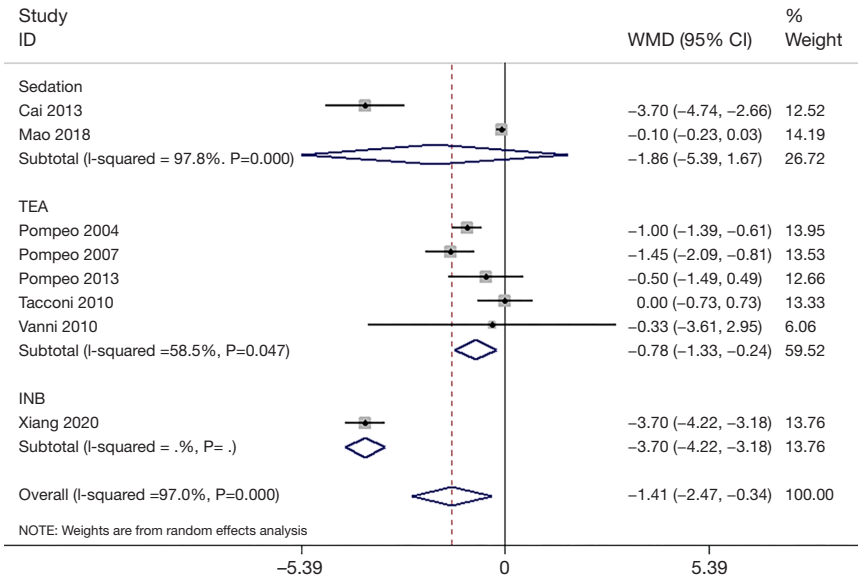

Figure 4 A forest plot showing the length of hospital stay for a subgroup analysis based on the mode of anesthesia delivery. TEA, thoracic epidural anesthesia; INB, intercostal nerve block; WMD, weighted mean difference; CI, confidence interval.

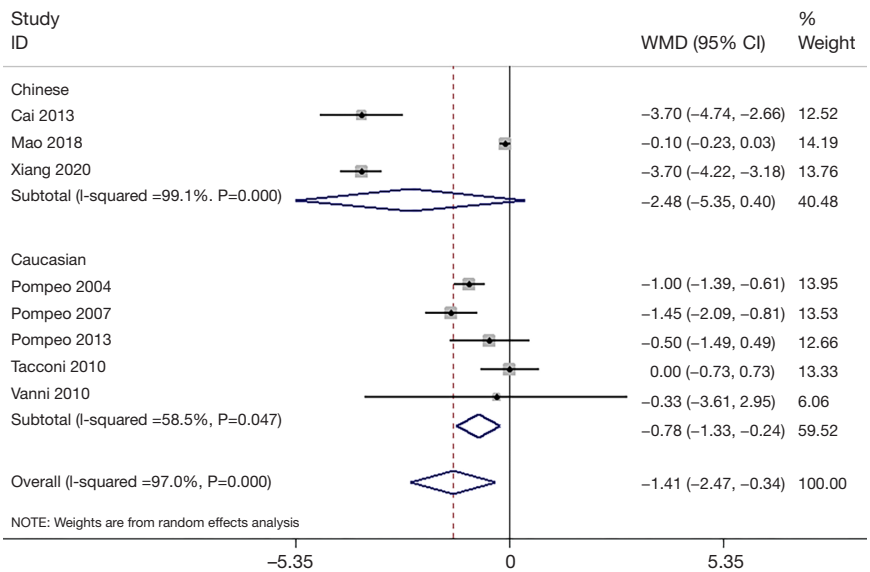

Figure 5 A forest plot showing the length of hospital stay for a subgroup analysis based on ethnicity. WMD, weighted mean difference; CI, confidence interval.

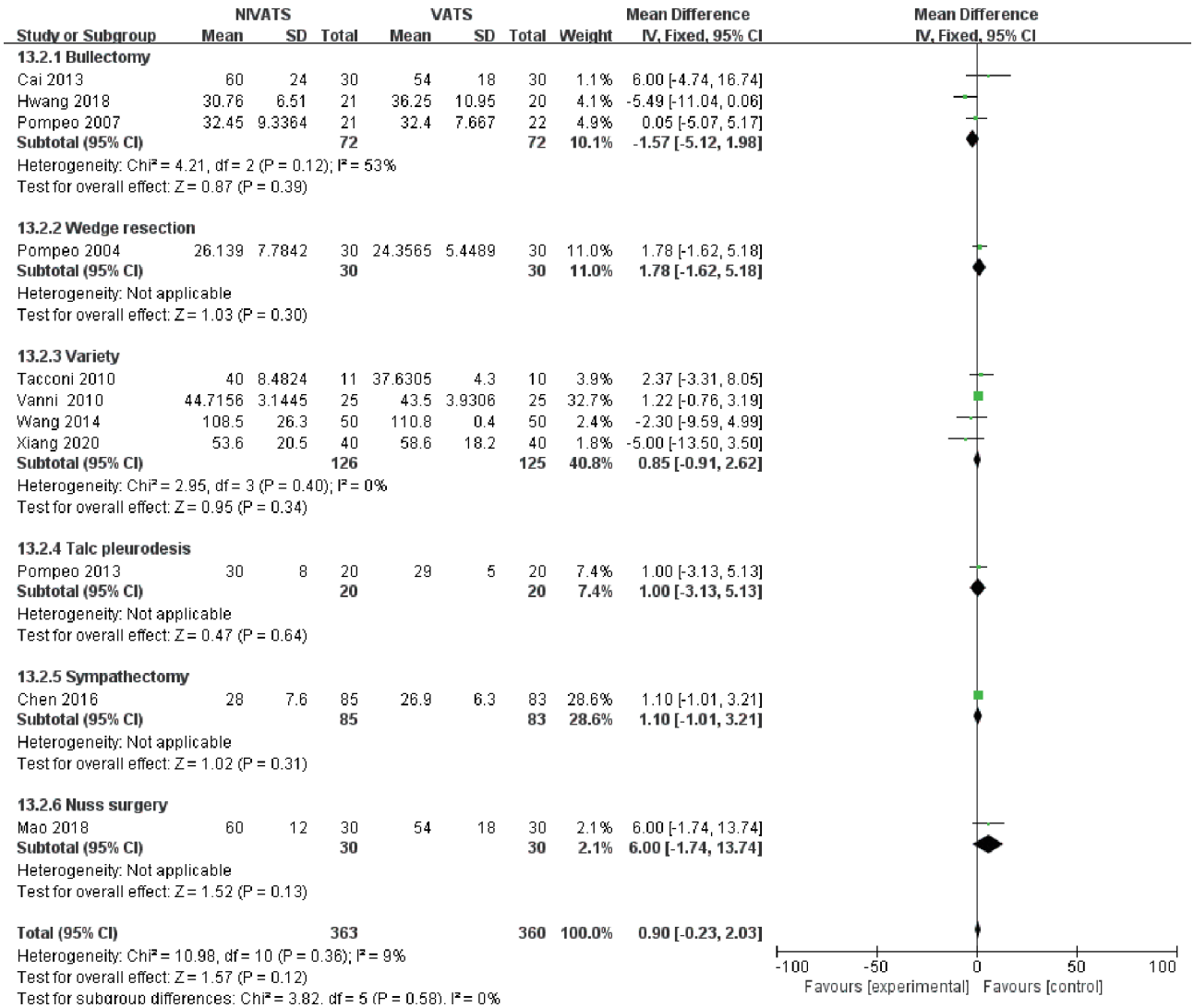

Figure 6 A forest plot is showing the difference in operation time between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; SD, standard deviation; IV, inverse variance; CI, confidence interval.

were combined with the fixed effects model, and this revealed that the operation time of non-intubated thoracoscopic surgery was not statistically different compared to patients with intubation (MD 0.90; 95% CI: −0.23 to 2.03; P=0.12). Subgroup analysis was carried out for the other 11 studies. No significant differences were observed compared to the original analysis (*Figure 6*). The funnel plot analysis showed that the operation time results are distributed symmetrically (*Figure 8*).

Surgical field satisfaction (1 point)

Surgical field satisfaction (1 point) was reported in three studies (17,29,30) with small inter-study heterogeneity (P=0.88, I^2 =0%). A surgical field satisfaction of 1 point denotes complete lung collapse with a well-exposed operative field. A score of 2 points denotes normal lung collapse with a relatively clear surgical field of vision, with no need to interrupt the operation. A score of 3 points represents a poor surgical field exposure with unsatisfactory lung collapse, necessitating repeated interruption to the surgery. A score of 4 points represents poor exposure to the surgical field and a failure to complete the operation, necessitating the transfer to intubation surgery. In all three

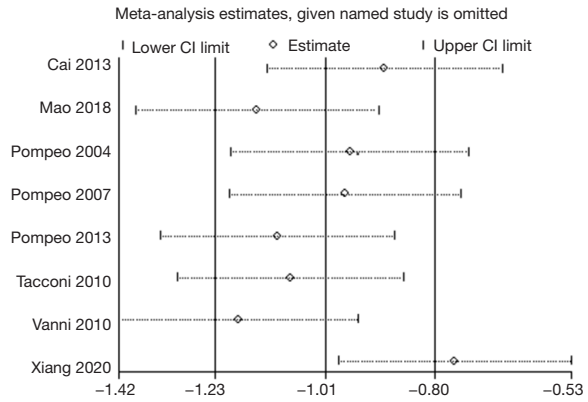

Figure 7 A sensitivity analysis of the length of hospital stay. CI, confidence interval.

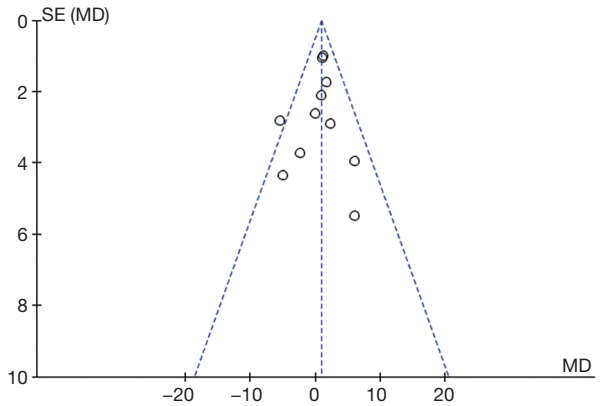

Figure 8 A funnel plot was showing the difference in operation time between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; SE, standard error; MD, mean difference.

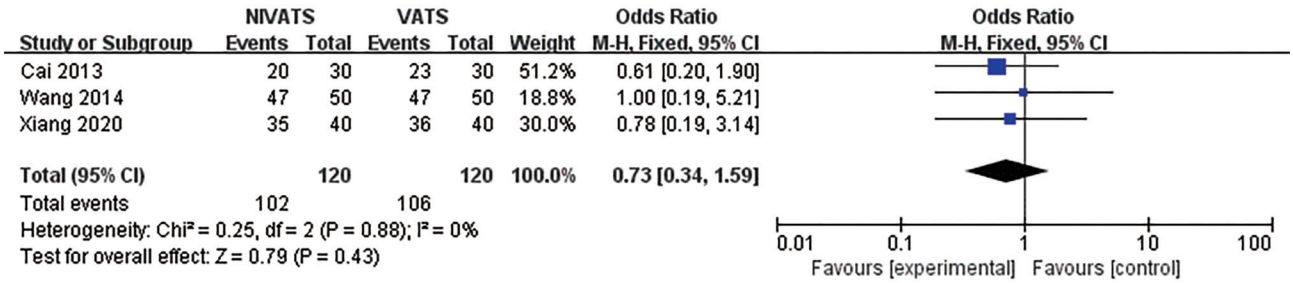

Figure 9 A forest plot shows the surgical field satisfaction (1 point) between the NIVATS and VATS groups. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

studies that reported the surgical field satisfaction, the patients' surgical field satisfaction was mostly 1 (complete lung collapse with a well-exposed operative field). The fixed effects model demonstrated that the difference in surgical field satisfaction between the NIVATS group and the VATS group was not statistically significant (OR 0.73; 95% CI: 0.34 to 1.59; P=0.43; *Figure 9*).

Anesthesia satisfaction scores

Anesthesia satisfaction scores were reported in four studies (23,24,26,27), with small inter-study heterogeneity (P=0.6, I^2 =0%). The fixed effects model revealed that anesthesia satisfaction scores in the NIVATS group were significantly higher than the VATS group (MD 0.50; 95% CI: 0.12 to 0.88; P=0.009; *Figure 10*).

VAS score

The VAS scores were reported in four studies (19,20,23,26), with little inter-study heterogeneity (P=0.53, I^2 =0%). The fixed effects model showed that the VAS scores in the NIVATS group were significantly lower than those in the VATS group (MD −0.34; 95% CI: −0.58 to −0.10; P=0.006; *Figure 11*).

Complications

The incidences of overall complications (OR 0.41; 95% CI: 0.25 to 0.67; P=0.0004), respiratory complications (OR 0.37; 95% CI: 0.21 to 0.66; P=0.0006) including air leakage (OR 0.45; 95% CI: 0.24 to 0.87; P=0.02), intubation-related complications (OR 0.07; 95% CI: 0.04 to 0.16; P<0.00001) including pharyngeal discomfort (OR 0.08; 95% CI: 0.04 to 0.17; P<0.00001) and hoarseness (OR 0.06; 95% CI: 0.02 to 0.21; P<0.00001), and gastrointestinal reactions (OR 0.23; 95% CI: 0.10 to 0.53; P=0.0005) were significantly lower in the NIVATS group compared to the VATS group. The incidences of postoperative atelectasis (OR 0.33; 95% CI: 0.06 to 1.65; P=0.18) and pulmonary infections (OR 0.40;

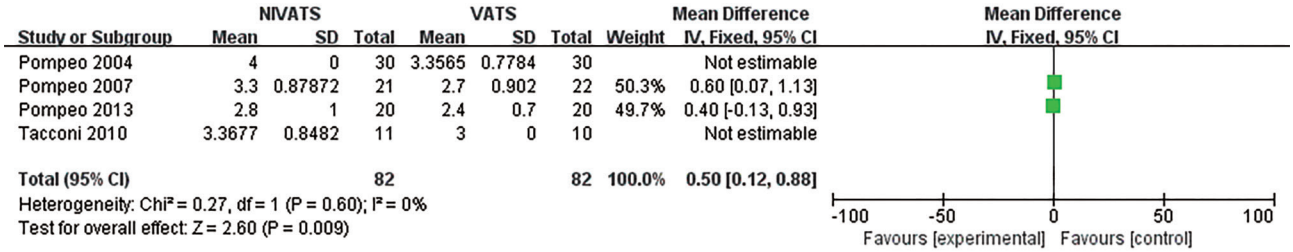

Figure 10 A forest plot showing the difference in the anesthesia satisfaction scores between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; SD, standard deviation; IV, inverse variance; CI, confidence interval.

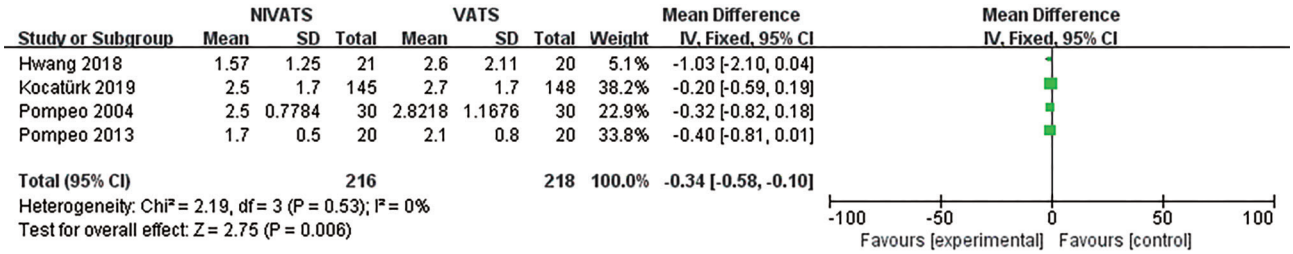

Figure 11 A forest plot showing the difference in the VAS scores between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; SD, standard deviation; IV, inverse variance; CI, confidence interval.

95% CI: 0.13 to 1.20; P=0.10) in the NIVATS group were not significantly different from those in the VATS group. All studies demonstrated small heterogeneity (P>0.01, I^2 =0%) and the fixed effects model was used for analysis (*Figures 12-20*).

Discussion

A total of 1,426 patients were included in 14 RCTs to evaluate the safety and efficacy of NIVATS. The random effects model analysis showed that the hospitalization time of patients in the NIVATS group was shorter than that of patients in the VATS group. However, the heterogeneity between studies was large, and this could not be resolved by using multiple subgroup analyses. This could be due to the large variety of diseases and surgical procedures presented in these studies, the small sample size, and the large variations in the length of hospital stay in each study. In addition to the type of operation, the postoperative chest-tube dwell time and the application of antibiotics can also affect hospital stay length. Furthermore, a patient's discharge may depend on the subjective assessment of a patient's rehabilitation status. Therefore, further large-scale studies are required to support the results of this meta-analysis.

This report's investigations demonstrated that there was no significant difference in the operation time and surgical field satisfaction between patients in the NIVATS group and the VATS group. However, in terms of the operation time, there was considerable heterogeneity among studies. Considering the variety of surgical procedures in the included studies, it cannot simply be assumed that the operation time in NIVATS patients would not be longer than that in VATS patients. Despite the risks of intraoperative mediastinal oscillation, cough, and insufficiency of lung collapse (31), the study showed that the surgeon's subjective satisfaction score with field conditions did not decrease in NIVATS. In the three studies that reported surgical field satisfaction, most of the patients in both groups had an surgical field satisfaction of 1 point, and no cases with poor surgical field conditions were reported. In recent years, serratus anterior block and spinal horizontal block have emerged as effective methods for reducing intraoperative pain (32). A degree

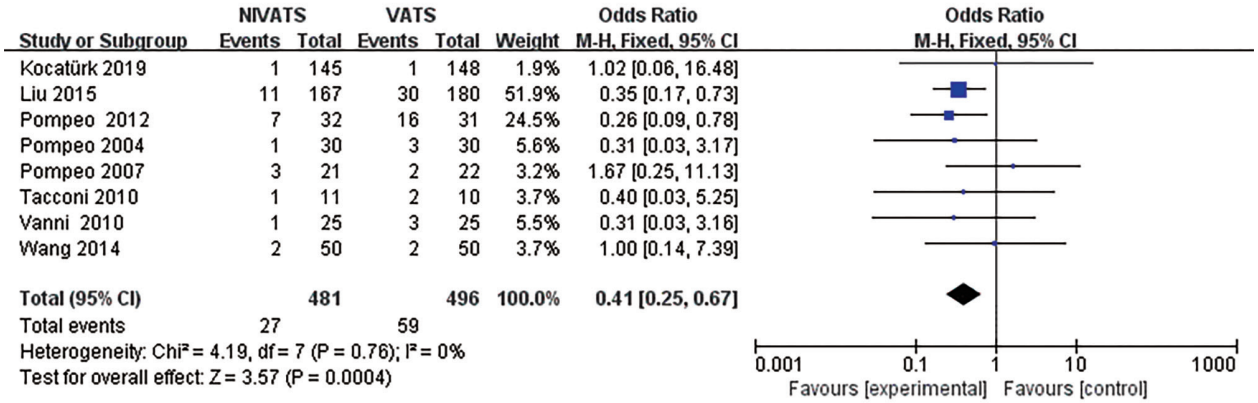

Figure 12 A forest plot showing the difference in the rate of overall complications between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

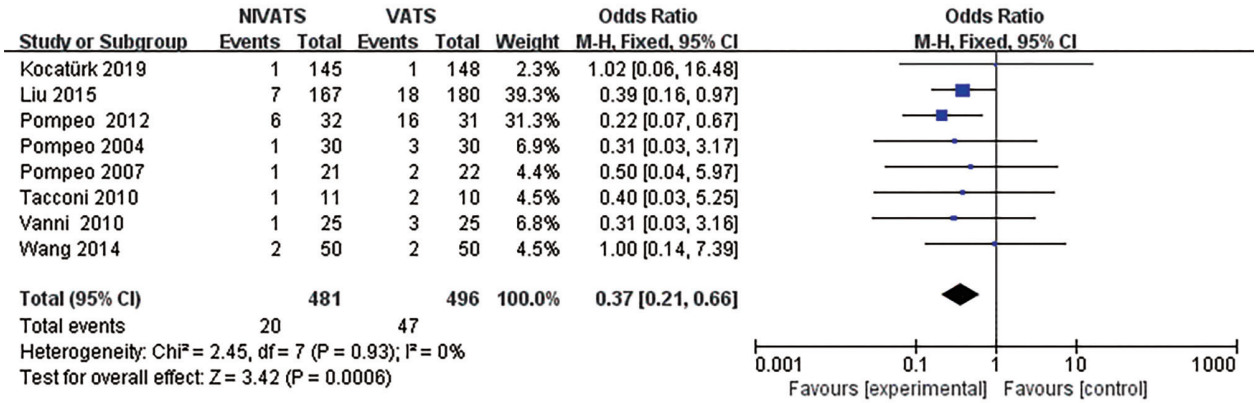

Figure 13 A forest plot showing the difference in the rate of respiratory complications between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

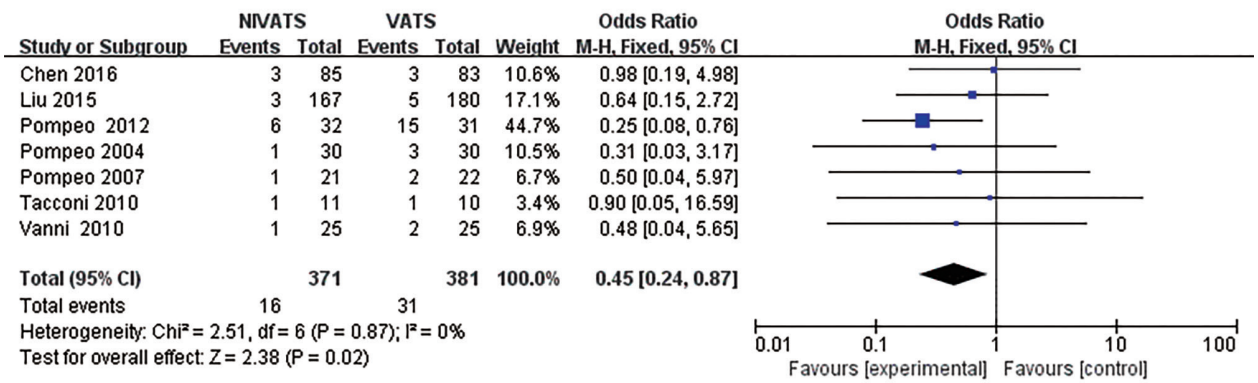

Figure 14 A forest plot showing the difference in the rate of air leak between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

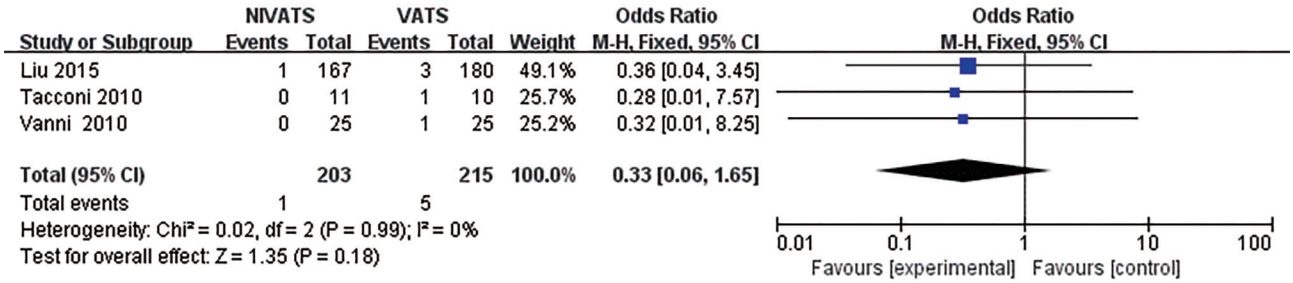

Figure 15 A forest plot shows the difference in postoperative atelectasis rate between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

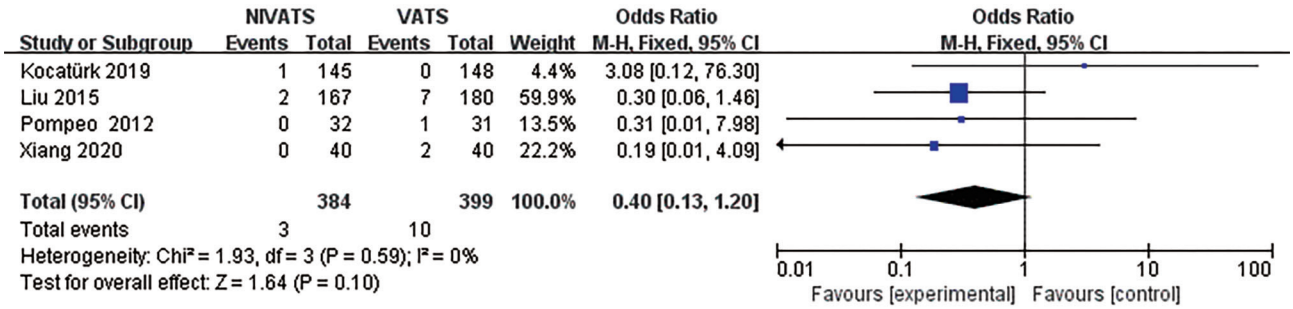

Figure 16 A forest plot shows the difference in pulmonary infection rate between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

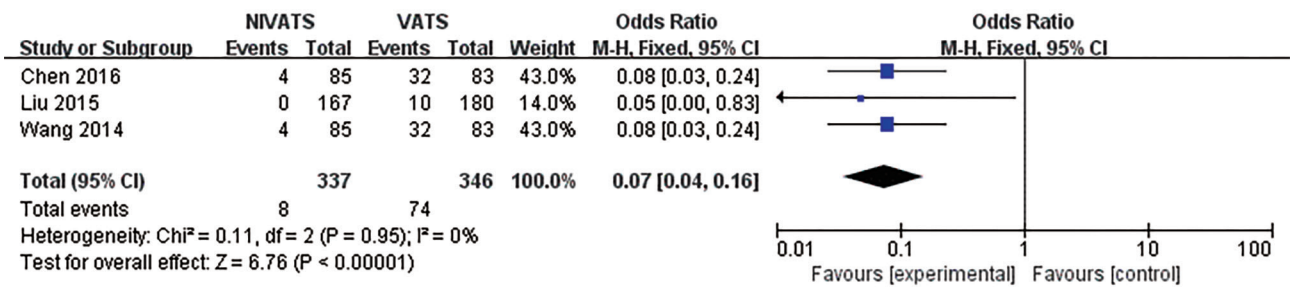

Figure 17 A forest plot showing the difference in the rate of intubation-related complications between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

of diaphragmatic movement and mediastinal movement is acceptable, although excessive mediastinal movement may affect surgical procedures (33). The length of the patient's operation time was not prolonged due to the improved surgical field conditions. This suggested that the selection of patients who strictly conform to the indications (34,35), combined with precise intraoperative anesthesia management and the surgeon's gentle and skilled operation, can achieve a surgical field experience comparable to that of conventional endotracheal intubation VATS.

Patients in the NIVATS group showed higher anesthesia satisfaction scores, which indicated that flexible and stable anesthesia management during NIVATS surgery enables patients to obtain better sedative and analgesic effects. Also,

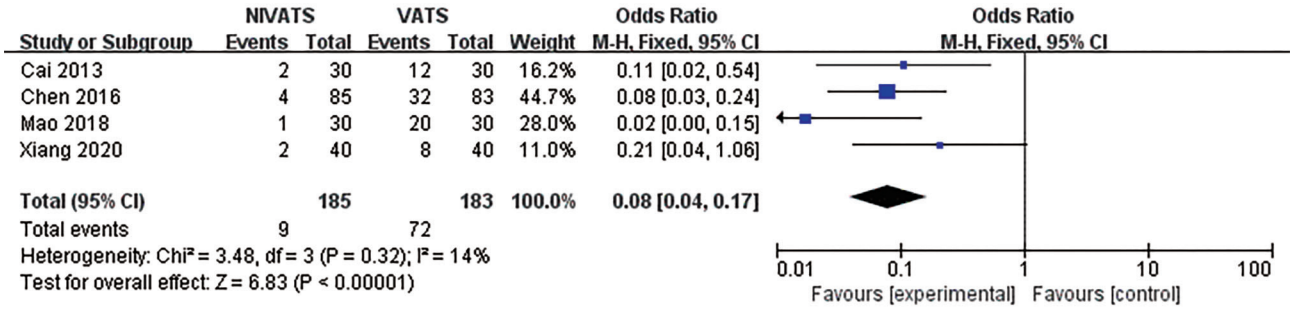

Figure 18 A forest plot showing the difference in the rate of pharyngeal discomfort between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

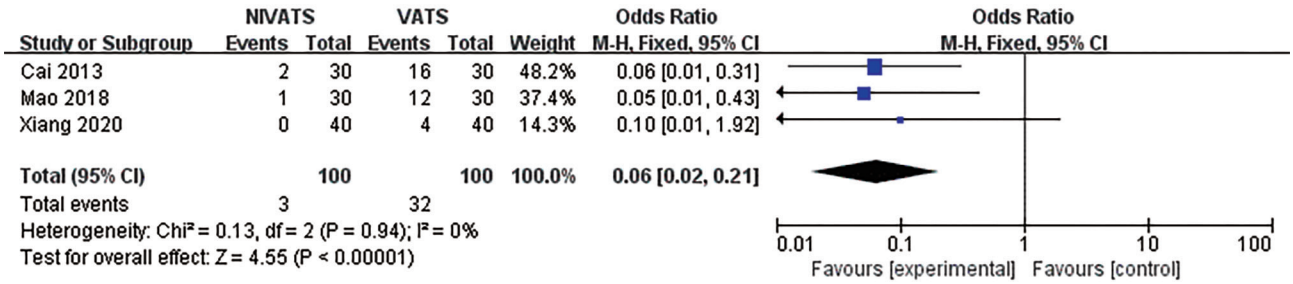

Figure 19 A forest plot showing the difference in the rate of hoarseness between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

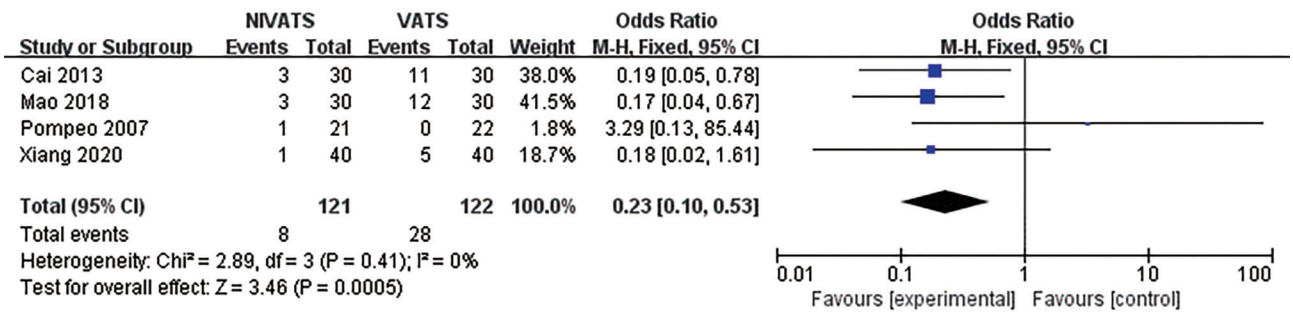

Figure 20 A forest plot showing the difference in the rate of gastrointestinal reactions between the NIVATS group and the VATS group. NIVATS, non-intubated video-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M-H, Mantel Haenszel; CI, confidence interval.

the pain associated with tracheal intubation and the residual effects of muscle relaxants were avoided, which may explain the lower VAS scores in patients in the NIVATS group than patients in the VATS group 24 hours after surgery.

In this study, the incidence of total complications in the NIVATS group was lower than that in the VATS group. Additionally, the incidences of respiratory complications (including postoperative pneumothorax, atelectasis, and pulmonary infection), intubation-related complications (including pharyngeal discomfort and hoarseness), and digestive tract reactions were lower in the non-intubated group compared to the intubated group. The differences

in the complication indexes were all statistically significant, except for atelectasis and pulmonary infection. A sensitivity analysis of postoperative air leakage was conducted. After removing the publication by Pompeo *et al.* (25), the initial results (P=0.02) were altered (P=0.25). However, the pneumothorax incidence in the NIVATS group was still lower than that in the VATS group, but the difference was not statistically significant. An analysis of the literature included in this study revealed a high incidence of air leakage in emphysema patients who had undergone lung volume reduction surgery. Mechanical ventilation with endotracheal intubation can result in pulmonary barotrauma, and regional hyperventilation can lead to alveolar rupture (36). Also, the opening and closing of the terminal bronchi and alveoli with ventilator-mediated ventilation can result in shear stress on lung tissue cells, namely, shear force injury. NIVATS avoids mechanical ventilation and can effectively reduce the incidence of pneumothorax after lung volume reduction surgery (37). However, with the exception of Liu *et al.* (21) and Pompeo *et al.* (25), there were no significant differences in the incidences of total complications and respiratory complications between NIVATS patients and VATS patients. This suggested that NIVATS mainly reduced the occurrence of hoarseness and pharyngeal discomfort, with no obvious advantages in air leakage, atelectasis, and other aspects. It is interesting to note that the VATS group experienced a high incidence of postoperative pharyngeal pain. Therefore, particular attention should be given to standardized endotracheal intubation requirements and to explore novel methods and techniques to reduce patient discomfort.

Colonized bacteria in the pharynx and larynx can enter the lower respiratory tract with tracheal intubation, causing opportunistic respiratory infections and postoperative symptoms such as sore throat, cough, and sputum (38). Also, residual muscle relaxants can delay the recovery time of patients' cough and sputum ability after surgery, leading to a series of complications such as postoperative atelectasis (39). A prospective study showed that the incidence of postoperative pharyngeal pain and hoarseness due to endotracheal intubation was 44% (40). However, Puri *et al.* (41) believed that inflation of the LMA capsule could cause a feeling of pharyngeal compression, and hence some patients may also experience postoperative pharyngeal pain, pharyngeal nerve compression injury, and other deficiencies. Our meta-analysis showed that the incidence of total intubation-related complications, pharyngeal discomfort, and hoarseness in the NIVATS group was lower than that in the VATS group, suggesting that non-intubation reduced postoperative pharyngeal pain and hoarseness.

Other studies (42) have shown that muscle relaxants significantly increase postoperative nausea and vomiting, leading to a high incidence of postoperative gastrointestinal reactions by reducing intestinal perfusion and oxygen delivery. Furthermore, systemic opioid analgesics can also inhibit gastrointestinal function. The data from this meta-analysis support this.

Previous meta-analyses showed that patients undergoing non-intubated thoracoscopic surgery had shorter hospital stays and postoperative fasting (43), less postoperative inflammation, and better immune function recovery (44). However, most of the included studies were retrospective studies, and the selection and reporting bias may have affected the study results. In the current meta-analysis, all included literature were RCTs to minimize the selection bias as much as possible. After the risk assessment of bias in all the literature, it was noted that most of the literature applied randomized grouping and blind methods, and therefore the risk of bias was lower.

The safety and efficacy of non-intubation thoracic surgery were assessed from the surgeon and the patient's perspective. The surgical environment of NIVATS was evaluated from the surgeon's perspective by the surgical field score, and the operation time was objectively measured. The anesthesia satisfaction score evaluated short-term postoperative pain, and the VAS score 24 hours after surgery. Indicators, including pharyngeal discomfort, hoarseness, and postoperative air leakage, were analyzed to evaluate the patients' perioperative rehabilitation quality. Combined with the overall length of hospital stay, the results demonstrated that NIVATS was beneficial to the patients' overall rehabilitation. However, a number of RCTs reported on anatomical resections such as lobectomy and segmentectomy. Therefore, further large-scale, high-quality clinical randomized trials are warranted.

Despite the advantages, NIVATS has certain shortcomings, such as intraoperative hypoxemia and hypercapnia, mediastinal oscillation, and cough reflex, and therefore some researchers have suggested that the value of NIVATS should be re-examined. As a novel method of anesthesia, NIVATS has stricter patient indications. Numerous studies have demonstrated that NIVATS avoids the complications of VATS and accelerates the patient's postoperative rehabilitation. It may indeed be a new option

for patients who cannot tolerate endotracheal intubation, such as patients with neck trauma requiring immobilization or patients with severe cervical spondylosis undergoing elective surgery. Further extensive research is warranted to understand the benefits and risks associated with NIVATS fully.

Conversion of NIVATS to VATS has been reported in two studies. Hung *et al*. (45) suggested that patients in NIVATS should be immediately transferred to tracheal intubation anesthesia in the following situations: (I) respiratory acidosis where pH <7.1; (II) hypoxemia (PO_2 <60 mmHg) with no improvement following high-flow oxygen inhalation and non-invasive ventilation; (III) continuous cough with no improvement following aerosolized lidocaine and vagus nerve block; (IV) anxiety attack and invalid sedation; (V) voluntary conversion of patients; and (VI) intraoperative massive hemorrhage. The long-term survival of NIVATS patients is also of concern. In 2012, Pompeo *et al*. reported that the rates of freedom from contralateral treatment in group NIVATS and VATS were 55% versus 50%, and survival rates were 81% versus 87% at 36 months. It will be beneficial for future investigations to examine long-term survival in NIVATS patients.

There are some limitations to this report. First, in some studies included in this investigation, risk bias evaluation factors such as random method, blind method, allocation, and hiding were not clearly described, which may affect the final research conclusion's authenticity. Second, due to the small number of included studies, the heterogeneity could not be reduced by subgroup analysis, and the heterogeneity was still large. Third, indications and contraindications were lacking in multi-center large sample prospective clinical studies, and therefore, the long-term benefits are not clear.

Conclusions

NIVATS can significantly reduce intubation-related complications, relieve postoperative pharyngeal and gastrointestinal discomfort, and reduce patients' postoperative VAS scores. NIVATS is a technology co-created by the thoracic surgery department and the anesthesiology department to pursue a "holistic minimally invasive strategy" and "ERAS". The aim is to minimize postoperative clinical management pressure and greatly reduce the patient's postoperative pain. To date, several studies have demonstrated that NIVATS is safe for use in a variety of chest diseases and may be an important development in the field of minimally invasive thoracic surgery in the future.

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Footnote

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