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REVIEW

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Non-intubated spontaneous ventilation in video-assisted thoracoscopic surgery: a meta-analysis

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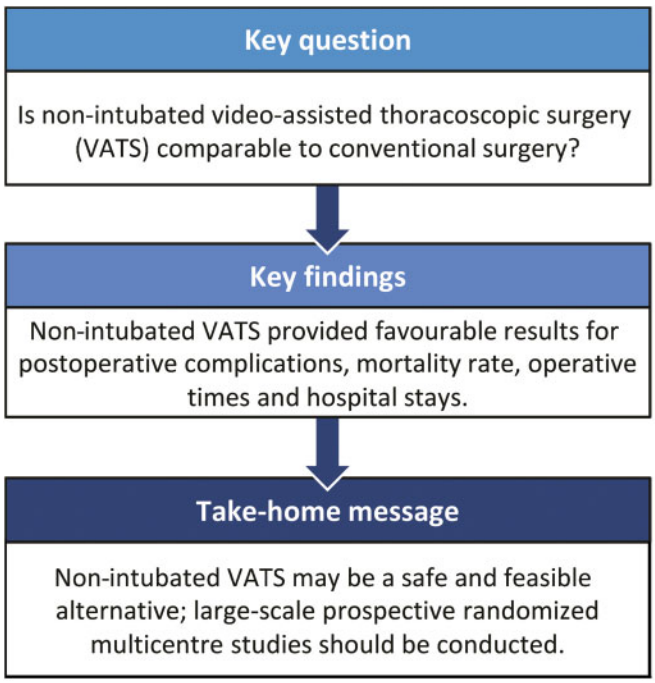

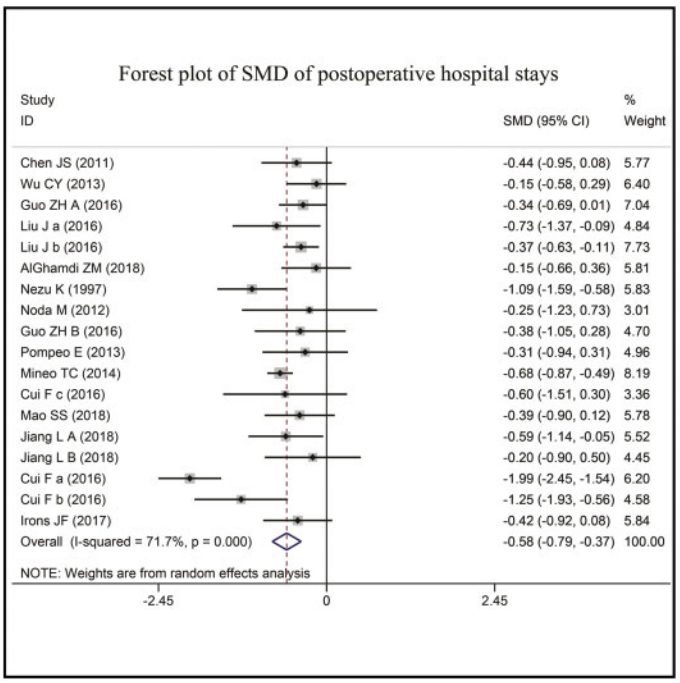

Summary

It remains unclear whether non-intubated video-assisted thoracoscopic surgery (VATS) is comparable or advantageous compared with conventional intubated VATS. Thus, we systematically assessed the feasibility and safety of non-intubated VATS compared with intubated VATS perioperatively for the treatment of different thoracic diseases. An extensive search of literature databases was conducted. Perioperative outcomes were compared between 2 types of operations. The time trend of the overall results was evaluated through a cumulative meta-analysis. Subgroup analyses of different thoracic diseases and study types were examined. Twenty-seven studies including 2537 patients were included in the analysis. A total of 1283 patients underwent non-intubated VATS; intubated VATS was performed on the other 1254 patients. Overall, the non-intubated VATS group had fewer postoperative overall complications [odds ratios (OR) 0.505;

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$P < 0.001$]; shorter postoperative fasting times [standardized mean difference (SMD) -2.653; $P < 0.001$]; shorter hospital stays (SMD -0.581; $P < 0.001$); shorter operative times (SMD -0.174; $P = 0.041$); shorter anaesthesia times (SMD -0.710; $P < 0.001$) and a lower mortality rate (OR 0.123; $P = 0.020$). Non-intubated VATS may be a safe and feasible alternative to intubated VATS and provide a more rapid postoperative rehabilitation time than conventional intubated VATS.

Keywords: Non-intubated video-assisted thoracoscopic surgery • Spontaneous ventilation • Perioperative outcomes • Meta-analysis

ABBREVIATIONS

CI	Confidence intervals
EA	Epidural anaesthesia
GA	General anaesthesia
OLV	One-lung ventilation
OR	Odds ratios
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
SMD	Standardized mean difference
VAS	Visual analogue scale
VATS	Video-assisted thoracoscopic surgery

INTRODUCTION

Minimally invasive procedures have been accepted in thoracic surgery since the last century. Double-lumen intubation-induced one-lung ventilation (OLV) in video-assisted thoracoscopic surgery (VATS) has been considered a safe and conventional practice in thoracic surgery worldwide, with less postoperative pain, fewer operative complications, shorter hospital stays and reduced costs.

Nevertheless, the adverse effects of conventional intubated VATS have aroused increasing attention in recent years. Simultaneously, various studies have confirmed that postoperative residual neuromuscular blockade resulting from the intubated VATS might lead to more respiratory complications and impaired clinical recovery [1, 2]. Thus, non-intubated spontaneous ventilation VATS has gained in popularity in the past decade because it could reduce adverse events caused by the regimens of intubated anaesthesia and OLV.

In 1997, Nezu *et al.* [3] initially assessed the perioperative outcomes of non-intubated VATS under spontaneous pneumothorax with local anaesthesia, declaring it a safe and beneficial alternative to intubated VATS with the patient under general anaesthesia (GA), with significantly shorter hospital stays and less invasion under simplified procedures. Since then, non-intubated VATS [3–29] has been successfully applied to various thoracic conditions, ranging from pneumothorax [6, 12, 20, 26], malignant pleural effusion [13, 15], parapneumonic empyema [7], resection of pulmonary nodule [4, 5, 10, 14, 19, 21, 22, 24, 25] to lung volume reduction [11], with the potential benefits including faster postoperative recovery times, fewer complications and shorter hospital stays [3–6, 10, 12, 14, 19–22, 24–26].

Overall, it remains unclear whether the efficacy of non-intubated VATS is comparable to or advantageous in contrast with conventional intubated VATS. Consequently, we performed this meta-analysis to assess the feasibility and safety of non-intubated VATS compared with intubated VATS perioperatively in the treatment of different thoracic diseases.

MATERIALS AND METHODS

Academic retrieval strategies

An overall retrieval of literature from network databases including PubMed, Embase, Web of Science, Cochrane Library and Google Scholar was conducted to identify all relevant studies published before October 2018. We amalgamated 'non-intubated' or 'awake' or 'tubeless' with 'intubated' and 'one-lung ventilation' or 'mechanical ventilation' and 'video-assisted thoracoscopic surgery' as well as their Medical Subject Headings (MeSH) terms. An additional manual search was conducted of the reference lists originating from retrieved review articles, primary studies and abstracts from conferences.

All retrieved results were assessed in the light of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The inclusion criteria are as follows: (i) comparisons between non-intubated VATS and intubated VATS; (ii) all patients who underwent the same surgical procedures except for the intubation, anaesthesia or ventilation; (iii) the studies that contained both randomized controlled trials (RCTs) and observational studies; (iv) studies in which at least 1 of the following target outcomes was mentioned, including the score on the visual analogue scale (VAS), operative time, anaesthesia time, postoperative fasting time, chest-tube time, hospital stay, conversion to thoracotomy, conversion to intubation, complication rate, death of blood loss; and (v) articles published or accepted in English that could be retrieved in the network databases mentioned above as of October 2018. The exclusion criteria were as follows: (i) no comparisons between non-intubated VATS and intubated VATS; (ii) except for the difference in intubation, anaesthesia or ventilation, other differences were observed during the surgical procedures; (iii) articles not written in English or that could not be retrieved from the network databases mentioned above; and (iv) none of the target outcomes mentioned above were mentioned in the study.

Data acquisition and quality assessment

Four investigators extracted the data independently (Y.W., G.Q., Z.L. and H.L.), and disagreements among the 4 reviewers were resolved through discussion and an eventual consensus. The results were reviewed by the senior investigator (W.L.). All available information regarding target outcomes was acquired and contained in a Microsoft Excel database. Basic data were recorded from each study: first author, year of publication, country, type of study, study period, disease, surgery procedures and number of patients. The following outcomes were obtained to compare 2 surgical procedures: operative time; anaesthesia time; blood loss; hospital stays; postoperative fasting time; VAS score; conversion rate; chest-tube dwell time; postoperative overall, respiratory and cardiovascular complications; and perioperative deaths.

We assessed the quality of the observational studies using the Newcastle-Ottawa Scale. A high-quality observational study was defined as a study with a quality score of ≥7 stars out of a total score of 0–9 stars. Simultaneously, the quality assessment of RCTs was carried out using the Jaded scale; an RCT study was considered high-quality if it had a score ≥3 points.

Statistical analyses

An overall meta-analysis was performed. Simultaneously, except for some studies from the original text that could not be categorized into specific disorders, all the remaining studies were classified into different types of thoracic diseases. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for categorical variables. As for the continuous outcomes, the standardized mean difference (SMD) with the 95% CI was calculated. Meanwhile, single-arm meta-analyses were conducted for them. We used the Cochran Q χ^2 test and the I^2 statistic to examine the heterogeneity across studies; statistical heterogeneity was considered an I^2 statistic ≥50%. A random-effects model was preferred if high heterogeneity ($P < 0.5$ or $I^2 > 50\%$) was observed; otherwise a fixed-effects model was adopted. In addition, subgroup analyses based on different thoracic diseases and study types were conducted. Publication bias was evaluated by Funnel plot tests, Begg's test and Egger's test. Sensitivity analysis was performed by removing each study sequentially. The statistical analyses were conducted using Stata software (version 12, StataCorp, TX, USA). All the *P*-values were 2-tailed; statistical significance was set as *P*-value <0.05.

RESULTS

Characteristics of the studies and quality assessment

A total of 316 studies were initially scanned from the previously mentioned 5 network databases as of October 2018. After further confirmation of the full texts, 27 studies with a total of 2537 patients receiving either non-intubated VATS or intubated VATS were included. After careful inspection of the studies conducted by the same authors, we found that no patients appeared in analyses more than once. These authors conducted their studies on different diseases or on 1 disease for different periods. The retrieval process regarding non-intubated VATS versus intubated VATS is elucidated in the PRISMA flow chart seen in Fig. 1.

Of the 27 included studies, 9 were RCTs and the remaining 18 were observational studies. The majority of the studies were performed in China ($n = 11$) and Italy ($n = 11$), with the remaining 5 from Japan ($n = 2$), Korea ($n = 2$) and the UK ($n = 1$). All studies were conducted after 2000 except 1, which was performed in 1997. According to the Newcastle-Ottawa Scale, all of the observational studies were deemed high quality; they scored ≥7 stars, and the Jaded scale demonstrated that 6 of 9 RCTs attained high quality by scoring 3 points. The basic characteristics of the included studies are listed in Table 1.

Overall meta-analysis

Twenty-seven studies with 2537 patients were included in the overall analysis. The overall results revealed that patients who received non-intubated VATS were associated with significantly shorter hospital stays (SMD -0.581, 95% CI -0.792 to -0.371; $P < 0.001$; $I^2 = 71.7\%$), shorter postoperative fasting times (SMD -2.653, 95% CI -3.047 to -2.259; $P < 0.001$; $I^2 = 67.6\%$), shorter anaesthesia times (SMD -0.710, 95% CI -1.050 to -0.369; $P < 0.001$; $I^2 = 79.9\%$), shorter operative times (SMD -0.174, 95% CI -0.340 to -0.007; $P = 0.041$; $I^2 = 59.4\%$), shorter chest-tube dwelling times (SMD -1.122, 95% CI -2.208 to -0.036; $P = 0.043$; $I^2 = 97.0\%$; *P* for heterogeneity < 0.001), lower overall complication rates (OR 0.505, 95% CI 0.384–0.665; $P < 0.001$; $I^2 = 0.0\%$), lower respiratory complication rates (OR 0.454, 95% CI 0.311–0.661; $P < 0.001$; $I^2 = 0.0\%$), lower perioperative mortality rates (OR 0.123, 95% CI 0.021–0.717; $P = 0.020$; $I^2 = 0.0\%$), lower VAS scores (SMD -0.639, 95% CI -0.869 to -0.408; $P < 0.001$; $I^2 = 0.0\%$) whereas the other results were comparable (Figs 2 and 3; Supplementary figures).

The single-arm meta-analysis demonstrated that the postoperative overall complication rates were 7.3% (95% CI 5.8–8.8%) and 20.3% (95% CI 15.2–25.4%); the postoperative hospital stays were 4.722 (95% CI 3.862–5.582) and 6.065 days (95% CI 4.997–7.133); the postoperative fasting times were 5.817 (95% CI 5.066–6.568) and 13.752 h (95% CI 11.598–15.905); and the operative times were 95.209 (95% CI 77.298–113.121) and 101.577 min (95% CI 77.664–125.490) in the non-intubated and intubated groups, respectively. In addition, the rate of conversion to intubation was 3.2% (95% CI 1.9–4.4%) in non-intubated group (Supplementary Material, Table S3).

Subgroup analysis of study types

Outcomes were classified into 2 subsets in light of the different study types (observational studies versus RCTs). Except for the operative times, hospital stays and mortality rates, other outcomes were similar in the 2 subgroups. According to the results of the RCTs, patients undergoing non-intubated VATS had lower VAS scores, fewer overall complications, fewer respiratory complications, shorter anaesthesia times and shorter postoperative fasting times whereas other outcomes had no statistical significance compared with the intubated VATS group. It is worth mentioning that there were many fewer RCTs than there were observational studies (9 vs 18), especially on important perioperative outcomes. For example, only 2 RCTs reported the outcome as the mean ± standard deviation for hospital stays whereas 16 observational studies evaluated it. The detailed results are summarized in Supplementary Material, Table S2.

Subgroup analysis of pulmonary nodules

Nine studies with 833 patients were included in this analysis. The results indicated that patients undergoing non-intubated VATS had significantly shorter hospital stays, shorter anaesthesia times, shorter postoperative fasting times and lower overall complication rates whereas the other outcomes were comparable. No perioperative deaths occurred with either procedure (Supplementary Material, Table S1).

Subgroup analysis of spontaneous pneumothorax

Five studies with 207 patients were included in this analysis. The results demonstrated that patients undergoing non-intubated VATS had significantly shorter anaesthesia times and shorter hospital stays whereas other outcomes were comparable. No perioperative deaths occurred with either procedure in 3 of the included 4 studies (Supplementary Material, Table S1).

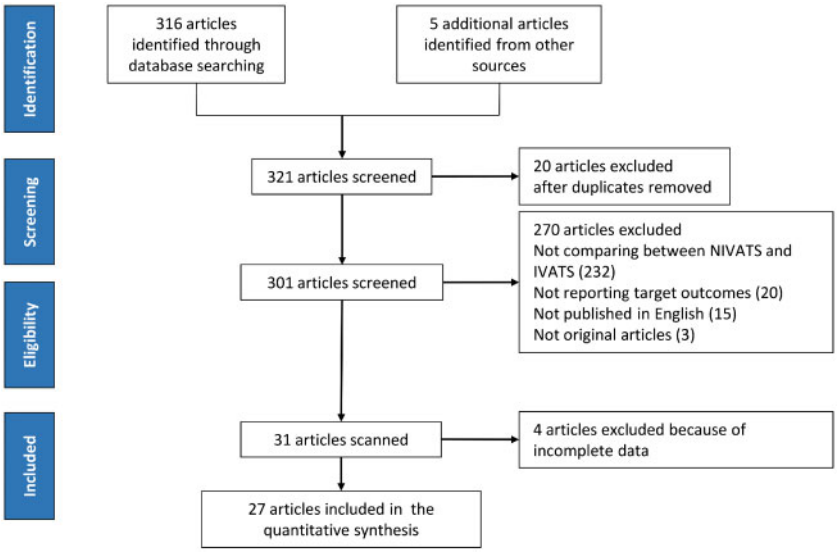

Figure 1: PRISMA flow diagram containing the search strategy and identification of studies used in meta-analysis.

Subgroup analysis of malignant pleural effusion

Two studies with 502 patients were included in this analysis. Patients undergoing non-intubated VATS had significantly shorter hospital stays and shorter anaesthesia times whereas other outcomes were comparable (Supplementary Material, Table S1).

Publication bias and sensitivity analysis

A sensitivity analysis was conducted by removing each included study sequentially in the overall analysis. The results showed that, with the exception of the operating times, chest-tube dwell time and the number of deaths, none of the removals changed the initial outcomes of the other analyses, indicating a valid stability of most of our outcomes. The funnel plots denoted symmetrical distributions for most outcomes (Supplementary figures). Results from Egger's test and Begg's test further corroborated that no publication bias occurred among the final outcomes. The exact outcomes are summarized in Supplementary Material, Table S4.

DISCUSSION

Conventionally, the VATS surgical procedures comprised GA and OLV through a double-lumen tube or an endobronchial blocker, used for creating an optimum surgical field and a quiet surgical environment [30]. However, the adverse events regarding the GA and OLV have aroused increasing concerns in the past decade. Consequently, the feasibility and safety of non-intubated VATS have been evaluated by surgeons globally in the past decade in the management of different thoracic conditions, reported primarily in small-scale RCTs, observational studies and case reports.

To date, 1 meta-analysis by Deng *et al.* [31] in 2016 assessed the perioperative outcomes of non-intubated VATS versus intubated VATS, comprising 10 studies with 1283 patients. More relative studies were updated over time, and more procedures like the trachea operation were no longer contraindicated [28]. Moreover, subgroup analyses of specific thoracic diseases were not included, which might lack guiding significance since the perioperative outcomes may vary in different thoracic diseases. It is time to update the systematic review to better highlight this technique. Compared with the previous study, our analysis comprised more of the latest studies, with a total of 27 studies including 2578 patients. Simultaneously, we compared more perioperative outcomes, ranging from postoperative fasting time, blood loss, anaesthesia time and specific respiratory complications to cardiovascular complications. Meanwhile, single-arm meta-analyses were also carried out to compare these 2 surgical procedures more comprehensively. Moreover, we conducted subgroup analyses in terms of different thoracic diseases to investigate the more favourable surgical procedure under different thoracic conditions.

In the overall meta-analysis, our results showed that non-intubated VATS was associated with significantly fewer postoperative overall complications, which could be explained by the following 3 perspectives. Since most of our included studies used epidural anaesthesia (EA), we focus mainly on EA. First, it is widely acknowledged that EA offers better pain control, enables patients to mobilize earlier and to take respiratory physiotherapy like deep breathing exercises and cough, which may contribute to increasing the residual pulmonary volume and hence prevent atelectasis, infections, small-airway closure and other pulmonary complications [32–41]. Meanwhile, alleviation of the inhibitory reflexes acting on the diaphragm and efficient mucociliary clearance resulting from EA may also help improve pulmonary function and hence give rise to fewer respiratory complications [35, 37, 42–44]. Second, by avoiding the use of muscle relaxants, we can prevent some adverse respiratory effects caused by residual muscle block, ranging from diaphragmatic dysfunction, weakness of the upper airway muscles and airway obstruction to hypoxaemia [1, 45]. Third, non-intubated VATS can prevent some side effects related to mechanical ventilation, ranging from ventilator-induced lung injury, ventilator-induced dysfunction of the diaphragm, throat pain and mucosal ulceration to bronchospasm [1, 46, 47].

The results of our study also indicated that the non-intubated VATS group had significantly shorter hospital stays compared with the intubated VATS group. The stays could be significantly

Table 1: Demographics of the included studies

Study	Country	Study type	Study period	Disease	Surgery procedures	Number of patients (cases/controls)	Propensity-matched	Quality score
Nezu *et al.* [3]	Japan	OS	1992–1995	Spontaneous pneumothorax	Bullectomy	32/38	No	NOS: 7
Pompeo *et al.* [4]	Italy	RCT	2001–2003	Pulmonary nodule	Wedge resection	30/30	No	Jaded score: 3
Pompeo and Mineo [5]	Italy	OS	2003–2005	Pulmonary nodule	Wedge resection	14/14	No	NOS: 8
Pompeo *et al.* [6]	Italy	RCT	2001–2005	Spontaneous pneumothorax	Bullectomy	21/22	No	Jaded score: 3
Tacconi *et al.* [7]	Italy	OS	2004–2008	Empyema thoracis	Pleural decortication	19/19	No	NOS: 8
Tacconi *et al.* [8]	Italy	RCT	2008–2009	Variety	Variety	11/10	No	Jaded score: 2
Vanni *et al.* [9]	Italy	RCT	2008–2009	Variety	Variety	25/25	No	Jaded score: 2
Chen *et al.* [10]	China	OS	2009–2010	Pulmonary nodule	Lobectomy	30/30	No	NOS: 8
Pompeo *et al.* [11]	Italy	OS	2007–2010	Emphysema	Lung volume reduction	41/19	No	NOS: 8
Noda *et al.* [12]	Japan	OS	2005–2010	Spontaneous pneumothorax	NA	15/42	Yes	NOS: 7
Pompeo *et al.* [13]	Italy	RCT	2007–2010	Malignant pleural effusion	Talc pleurodesis	20/20	No	Jaded score: 2
Wu *et al.* [14]	China	OS	2009–2011	Pulmonary nodule	Lobectomy	36/48	No	NOS: 8
Mineo *et al.* [15]	Italy	OS	2002–2012	Malignant pleural effusion	Talc pleurodesis	231/231	Yes	NOS: 8
Wang *et al.* [16]	China	RCT	NA	Variety	Variety	50/50	No	Jaded score: 3
Liu *et al.* [17]	China	RCT	2011–2012	Variety	Bullectomy/wedge resection/ lobectomy	167/180	No	Jaded score: 3
Cui *et al.* [18]	China	OS	2012–2015	Variety	Sympathectomy/bullectomy/ mediastinal tumour resection	89/82	No	NOS: 7
Guo *et al.* [19]	China	OS	2011–2015	Pulmonary nodule	Segmentectomy	48/92	No	NOS: 7
Guo *et al.* [20]	China	OS	2011–2015	Spontaneous pneumothorax	Bullectomy	15/22	No	NOS: 8
Liu *et al.* [21]	China	OS	2011–2014	Pulmonary nodule	Lobectomy	136/136	Yes	NOS: 8
Ambrogi *et al.* [22]	Italy	OS	2005–2014	Pulmonary nodule	Wedge resection	48/13	No	NOS: 8
Irons *et al.* [23]	the UK	OS	2015	Variety	Variety	31/31	Yes	NOS: 7
Mineo *et al.* [24]	Italy	OS	2005–2015	Pulmonary nodule	Wedge resection	55/13	No	NOS: 8
AlGhamdi *et al.* [25]	Korea	OS	2016	Pulmonary nodule	Lobectomy	30/30	No	NOS: 8
Hwang *et al.* [26]	Korea	RCT	2014–2015	Spontaneous pneumothorax	Bullectomy	21/20	No	Jaded score: 3
Jiang *et al.* [27]	China	OS	2009–2016	Myasthenia gravis	Thymectomy	27/27	Yes	NOS: 8
Jiang *et al.* [28]	China	OS	2014–2016	Tracheal tumours	Tracheal and carinal resection and reconstruction	18/14	No	NOS: 7
Mao *et al.* [29]	China	RCT	2016–2017	Pectus excavatum	Nuss surgery	30/30	No	Jaded score: 3

NA: not applicable; NOS: Newcastle-Ottawa Scale; OS: overall survival; RCT: randomized controlled trial.

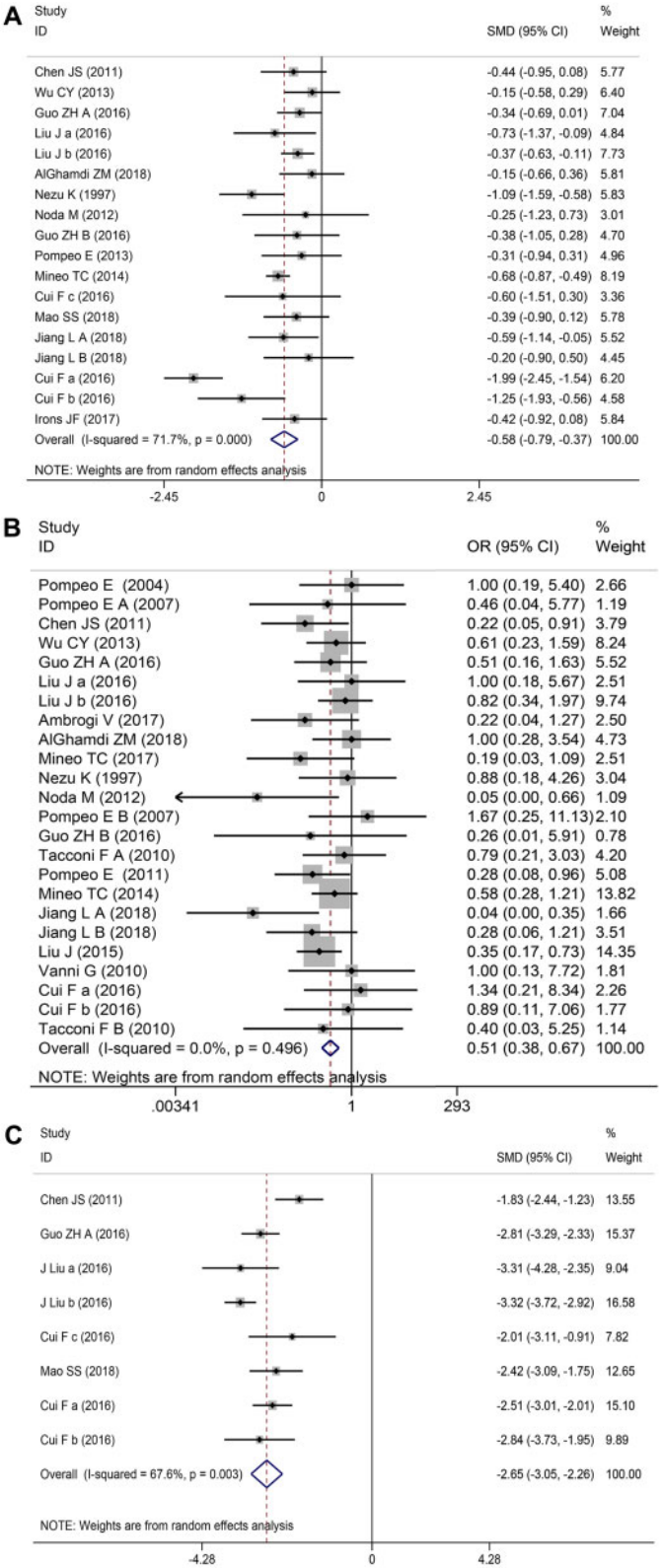

Figure 2: Forest plot of meta-analysis in main outcomes. (**A**) Forest plot of SMD of postoperative hospital stays. (**B**) Forest plot of OR of postoperative overall complication rate. (**C**) Forest plot of SMD of postoperative fasting time. CI: confidence intervals; OR: odds ratios; SMD: standardized mean difference.

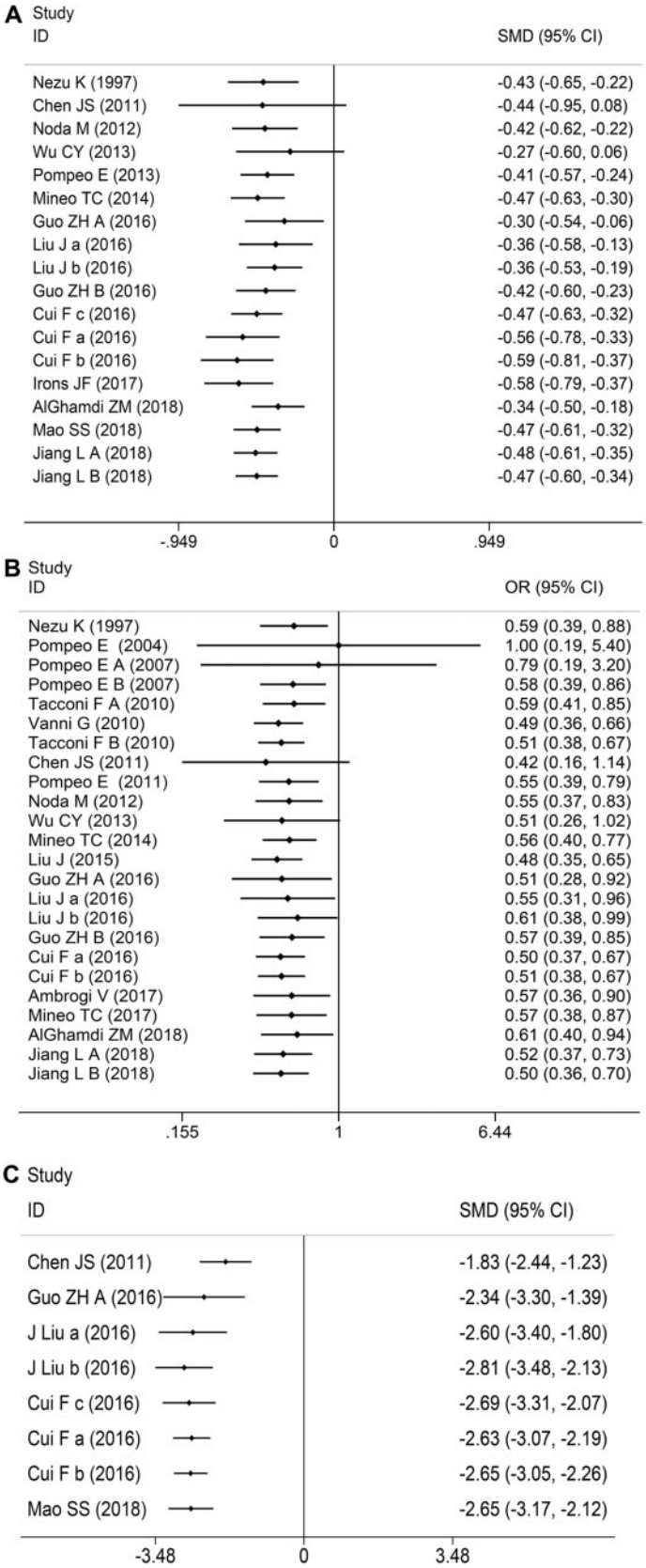

Figure 3: Cumulative meta-analysis in main outcomes. (**A**) Cumulative meta-analysis of postoperative hospital stays. (**B**) Cumulative meta-analysis of postoperative overall complication rate. (**C**) Cumulative meta-analysis of postoperative fasting time. CI: confidence intervals; OR: odds ratios; SMD: standardized mean difference.

shortened by reducing the overall complications mentioned previously. Simultaneously, hospital stays can also be shortened [2] by avoiding muscle relaxants, which result in muscle weakness and impaired clinical recovery. Previous researchers have argued that some GA agents might result in morbidity after gastrointestinal surgery by diminishing intestinal perfusion and oxygen delivery, and systemic opioid-based analgesics were confirmed to depress gastrointestinal function [48, 49]. Meanwhile, EA may lead to the accelerated recovery of gastrointestinal function by blockade of both the afferent and efferent limbs of the spinal reflex arc and the stress-related inhibitory output of the thoracolumbar sympathetic efferent. Furthermore, the increased colonic blood flow caused by sympathetic blockade is also considered a potentially positive factor for improving the gastrointestinal function [50]. Eventually, the shorter time under anaesthesia in the non-intubated VATS group could be easily interpreted as being due to the fact that, with non-intubated anaesthesia, there is no need to carry out tracheal intubation and bronchoscopic examinations and hence it can save time [31].

Though non-intubated VATS exhibited the better outcomes mentioned previously compared with conventional intubated VATS, it is not risk-free and has more difficult technical requirements for surgeons. First, during the process of non-intubated VATS, an open pneumothorax is created to induce a drop in lung volume to create adequate space to perform the operation. Nevertheless, for patients with pleural adhesions and emphysema-related lung hyperinflation, its extent can be greatly limited [51]. Second, open pneumothorax itself can result in impaired ventilation and oxygenation. During expiration, some of the exhaled gases move from the dependent lung to the nondependent lung, contributing to hypoxia and hypercapnia. Fortunately, such complications are usually mild and well-tolerated, and oxygenation is usually satisfactory through supplemental oxygen with a face mask [51]. For thoracic surgeons, such pendular ventilation results from spontaneous ventilation will increase the surgical difficulty since it may lead to the movement and inadequate collapse of the nondependent lung [10, 30, 51]. Moreover, the depth of anaesthesia should be balanced appropriately [25]. For example, with light anaesthesia, patients' oxygenation can be fully guaranteed but it is difficult for surgeons to operate on an extensively moving lung. Consequently, to make an accurate dissection, the surgeon must identify the appropriate depth of anaesthesia that maintains the balance of oxygenation and an adequate view of the surgical filed and then adjust the instruments and scope according to the rhythm of the patient's breathing. Generally, the collapse of a lung is controllable and its movement would not have much of an effect on the surgical procedure and perioperative outcomes [10].

In addition, the use of EA raises several concerns. First, it can result in spinal cord injury [52], probably due to the direct nerve trauma caused by the insertion of the needle or the injection of irritant drugs [51]. According to Parker [53], the sympathectomy induced by the EA can lead to a slower heart rate, reduced systemic vascular resistance and then hypotension. Second, nausea and vomiting can also occur after the use of EA in many patients, probably due to the hypotension caused by the sympathetic blockade and the unopposed parasympathetic response of increased peristalsis. Third, it is worth mentioning that the additional effects on motor function and sympathetic innervation of EA will influence pulmonary function though these effects are small compared with those without EA. Fourth, sympathetic blockade caused by EA can result in increased bronchial tone, airway hyper-reactivity and then a cough reflex, leading to interference with the division of the hilar vessels and bronchus and then some dangerous complications requiring conversion to GA with intubation or even thoracotomy [10]. Fifth, though it has been proved that EA improves postoperative analgesia under VATS, the use of opioids in the epidural infusion, such as fentanyl and sufentanil, may result in some side effects, ranging from pruritus, nausea and vomiting and urinary retention to respiratory depression [54], which can also impair postoperative recovery. In addition, opioid tolerance and opioid-induced hyperalgesia may be induced through the use of high-dose opioids perioperatively, leading to increased intensity in the perception of postoperative pain, which occurs more frequent than previously thought [55]. Consequently, other opioid-sparing alternatives should be explored and used in the future. Sixth, EA may also harm patients with anticoagulant therapy because of the risk of haemorrhagic complications [51]. Other complications include epidural haematoma, acute transverse myelitis or even paraplegia [56, 57].

Other anaesthetic approaches include vagus nerve block, paravertebral nerve block and intercostal nerve block; they are usually combined with other approaches for a better result. Six of our included studies combined the use of EA and vagus nerve block. As mentioned previously, the cough reflex cannot be blocked effectively by EA and can lead to severe complications. With the use of an intrathoracic vagal blockade, we can effectively abolish the cough reflex and hence easily prevent such complications [10, 14]. Four of our included studies adopted the intercostal nerve block, which was proved to be as safe and effective as EA in the treatment of lung cancer. It is easier and faster with less interference with intraoperative haemodynamics and is considered an alternative to EA for those who have contraindications for epidural catheterization and who are concerned about the risk of spinal cord injury [58]. One of our included studies used the paravertebral nerve block. Compared with EA, it is easier for surgeons to learn; provides comparable pain relief and the benefit of a unilateral block without bilateral sympathectomy; and has a lower incidence of hypotension, urinary retention and pulmonary complications. A recent study demonstrated that paravertebral nerve block is associated with decreased opioid use, which may be a better alternative than EA because of the lower risk of opioid use [59]. It can also be an alternative for those in whom epidural catheterization is contraindicated and extend the indications for non-intubated VATS [57]. Our centre is trying to use wound infiltration, intercostal nerve blockade and paravertebral blockade to eliminate the need for EA. Overall, the optimal anaesthetic method for non-intubated VATS is still a topic of debate. Other approaches are worth more attention and exploration for their potential benefit compared with EA.

Limitations

Several limitations in our study cannot be neglected. First, our meta-analysis comprised both observational studies and RCT studies, which could reduce the credibility of our study since these 2 different types of studies often manifest different results. Second, most of our included studies comprised retrospective nonrandomized comparisons, which might lead to the additional risk of potential selection and reporting bias. Surgeon bias could also

occur in our included non-randomized studies. However, 10 [7, 10, 15, 18–21, 23, 25, 28] of our 18 included non-randomized studies claimed that both surgical procedures were conducted by the same surgeon or the same team, which could reduce the bias to some extent. In addition, a recent study conducted by our centre in which the surgeon was added as a variable in propensity score matching demonstrated that non-intubated VATS showed significant benefits in terms of anaesthesia time, operative times, hospital stays and chest-tube durations [60]. Third, according to the results of the RCTs, we found that non-intubated VATS only showed benefit on the VAS score, overall complications, respiratory complications, anaesthesia times and postoperative fasting times compared with intubated VATS. Besides, there were many fewer RCTs reporting each outcome compared with overall survival rates. Consequently, the actual benefit of non-intubated VATS should be further validated in more RCTs. Fourth, some of our results had high heterogeneity. To explore its sources, we conducted subgroup analyses and found that it could be explained by the inter-group differences caused by different thoracic diseases requiring different surgical procedures. Fifth, since long-term outcomes such as recurrence and overall survival rates were reported only rarely, we were unable to evaluate more comprehensively the difference between these 2 procedures.

Thus, though our study has confirmed several benefits of the use of non-intubated VATS, there are still some gaps that we need to improve further. First, since most of our included studies were observational studies, there is a strong need for carrying out multicentre RCTs with large samples in the future. Second, many of our included studies did not clarify the specific disease, which might lack guiding significance under particular diseases. Thus, future studies should focus more on the practices of a specific type of disease or procedure. Third, due to the lack of long-term comparisons between these 2 procedures, more studies centring on long-term outcomes are strongly needed.

CONCLUSION

Generally, non-intubated VATS may be a safe and feasible alternative to intubated VATS with OLV and provide more rapid postoperative rehabilitation than intubated VATS in terms of the favourable results for postoperative fasting times, complication rates and hospital stays. Future large-scale prospective randomized multicentre studies are needed for validation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Yaokai Wen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—Original Draft; Writing—Review & Editing. **Hengrui Liang:** Conceptualization; Data curation; Investigation; Methodology; Validation; Writing—Original Draft; Writing—Review & Editing. **Guanping Qiu:** Data curation; Formal analysis; Investigation; Methodology; Writing—Original Draft; Writing—Review & Editing. **Zhichao Liu:** Data curation; Investigation; Writing - Review & Editing. **Jun Liu:** Validation; Writing - Review & Editing. **Weiqiang Ying:** Writing—Original Draft; Writing—Review & Editing. **Wenhua Liang:** Funding acquisition; Validation; Supervision; Writing - Review & Editing. **Jianxing He:** Funding acquisition; Project administration; Resources; Supervision; Validation; Writing - Review & Editing.

REFERENCES

[1] Gonzalez-Rivas D, Bonome C, Fieira E, Aymerich H, Fernandez R, Delgado M. Non-intubated video-assisted thoracoscopic lung resections: the future of thoracic surgery? Eur J Cardiothorac Surg 2016;49:721–31.
[2] Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS *et al*. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. Anesth Analg 2013;117:133–41.
[3] Nezu K, Kushibe K, Tojo T, Takahama M, Kitamura S. Thoracoscopic wedge resection of blebs under local anesthesia with sedation for treatment of a spontaneous pneumothorax. Chest 1997;111:230–5.
[4] Pompeo E, Mineo D, Rogliani P, Sabato AF, Mineo TC. Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules. Ann Thorac Surg 2004;78:1761–8.
[5] Pompeo E, Mineo TC. Awake pulmonary metastasectomy. J Thorac Cardiovasc Surg 2007;133:960–6.
[6] Pompeo E, Tacconi F, Mineo D, Mineo TC. The role of awake video-assisted thoracoscopic surgery in spontaneous pneumothorax. J Thorac Cardiovasc Surg 2007;133:786–90.
[7] Tacconi F, Pompeo E, Fabbi E, Mineo TC. Awake video-assisted pleural decortication for empyema thoracis. Eur J Cardiothorac Surg 2010;37:594–601.
[8] Tacconi F, Pompeo E, Sellitri F, Mineo TC. Surgical stress hormones response is reduced after awake videothoracoscopy. Interact CardioVasc Thorac Surg 2010;10:666–71.
[9] Vanni G, Tacconi F, Sellitri F, Ambrogi V, Mineo TC, Pompeo E. Impact of awake videothoracoscopic surgery on postoperative lymphocyte responses. Ann Thorac Surg 2010;90:973–8.
[10] Chen JS, Cheng YJ, Hung MH, Tseng YD, Chen KC, Lee YC. Nonintubated thoracoscopic lobectomy for lung cancer. Ann Surg 2011;254:1038–43.
[11] Pompeo E, Tacconi F, Mineo TC. Comparative results of non-resectional lung volume reduction performed by awake or non-awake anesthesia. Eur J Cardiothorac Surg 2011;39:e51–8.
[12] Noda M, Okada Y, Maeda S, Sado T, Sakurada A, Hoshikawa Y *et al*. Is there a benefit of awake thoracoscopic surgery in patients with secondary spontaneous pneumothorax? J Thorac Cardiovasc Surg 2012;143:613–16.
[13] Pompeo E, Dauri M; Awake Thoracic Surgery Research Group. Is there any benefit in using awake anesthesia with thoracic epidural in thoracoscopic talc pleurodesis? J Thorac Cardiovasc Surg 2013;146:495–7.e491.
[14] Wu CY, Chen JS, Lin YS, Tsai TM, Hung MH, Chan KC *et al*. Feasibility and safety of non-intubated thoracoscopic lobectomy for geriatric lung cancer patients. Ann Thorac Surg 2013;95:405–11.
[15] Mineo TC, Sellitri F, Tacconi F, Ambrogi V. Quality of life and outcomes after non-intubated versus intubated video-thoracoscopic pleurodesis for malignant pleural effusion: comparison by a case-matched study. J Palliat Med 2014;17:761–8.
[16] Wang S, Zhang J, Cheng H, Yin J, Liu X. A clinical evaluation of the ProSeal laryngeal mask airway with a Coopdech bronchial blocker for one-lung ventilation in adults. J Cardiothorac Vasc Anesth 2014;28:900–3.
[17] Liu J, Cui F, Li S, Chen H, Shao W, Liang L *et al*. Nonintubated video-assisted thoracoscopic surgery under epidural anesthesia compared with conventional anesthetic option: a randomized control study. Surg Innov 2015;22:123–30.
[18] Cui F, Liu J, Li S, Yin W, Xin X, Shao W *et al*. Tubeless video-assisted thoracoscopic surgery (VATS) under non-intubated, intravenous anesthesia

with spontaneous ventilation and no placement of chest tube postoperatively. J Thorac Dis 2016;8:2226–32.
[19] Guo Z, Yin W, Pan H, Zhang X, Xu X, Shao W *et al*. Video-assisted thoracoscopic surgery segmentectomy by non-intubated or intubated anesthesia: a comparative analysis of short-term outcome. J Thorac Dis 2016; 8:359–68.
[20] Guo Z, Yin W, Zhang X, Xu X, Liu H, Shao W *et al*. Primary spontaneous pneumothorax: simultaneous treatment by bilateral non-intubated videothoracoscopy. Interact CardioVasc Thorac Surg 2016;23: 196–201.
[21] Liu J, Cui F, Pompeo E, Gonzalez-Rivas D, Chen H, Yin W *et al*. The impact of non-intubated versus intubated anaesthesia on early outcomes of video-assisted thoracoscopic anatomical resection in non-small-cell lung cancer: a propensity score matching analysis. Eur J Cardiothorac Surg 2016;50:920–5.
[22] Ambrogi V, Sellitri F, Perroni G, Schillaci O, Mineo TC. Uniportal video-assisted thoracic surgery colorectal lung metastasectomy in non-intubated anesthesia. J Thorac Dis 2017;9:254–61.
[23] Irons JF, Miles LF, Joshi KR, Klein AA, Scarci M, Solli P *et al*. Intubated versus non-intubated general anesthesia for video-assisted thoracoscopic surgery—a case-control study. J Cardiothorac Vasc Anesth 2017; 31:411–17.
[24] Mineo TC, Sellitri F, Vanni G, Gallina FT, Ambrogi V. Immunological and inflammatory impact of non-intubated lung metastasectomy. Int J Mol Sci 2017;18:1466.
[25] AlGhamdi ZM, Lynhiavu L, Moon YK, Moon MH, Ahn S, Kim Y *et al*. Comparison of non-intubated versus intubated video-assisted thoracoscopic lobectomy for lung cancer. J Thorac Dis 2018;10:4236–43.
[26] Hwang J, Shin JS, Son JH, Min TJ. Non-intubated thoracoscopic bullectomy under sedation is safe and comfortable in the perioperative period. J Thorac Dis 2018;10:1703–10.
[27] Jiang L, Depypere L, Rocco G, Chen JS, Liu J, Shao W *et al*. Spontaneous ventilation thoracoscopic thymectomy without muscle relaxant for myasthenia gravis: comparison with "standard" thoracoscopic thymectomy. J Thorac Cardiovasc Surg 2018;155:1882–9.e1883.
[28] Jiang L, Liu J, Gonzalez-Rivas D, Shargall Y, Kolb M, Shao W *et al*. Thoracoscopic surgery for tracheal and carinal resection and reconstruction under spontaneous ventilation. J Thorac Cardiovasc Surg 2018;155: 2746–54.
[29] Mao S, Du X, Ma J, Zhang G, Cui J. A comparison between laryngeal mask airway and endotracheal intubation for anaesthesia in adult patients undergoing NUSS procedure. J Thorac Dis 2018;10:3216–24.
[30] Hung MH, Hsu HH, Cheng YJ, Chen JS. Nonintubated thoracoscopic surgery: state of the art and future directions. J Thorac Dis 2014;6: 2–9.
[31] Deng HY, Zhu ZJ, Wang YC, Wang WP, Ni PZ, Chen LQ. Non-intubated video-assisted thoracoscopic surgery under loco-regional anaesthesia for thoracic surgery: a meta-analysis. Interact CardioVasc Thorac Surg 2016;23:31–40.
[32] Kopeika U, Taivans I, Ūdre S, Jakušenko N, Strazda G, Mihelsons M. Effects of the prolonged thoracic epidural analgesia on ventilation function and complication rate after the lung cancer surgery. Medicina (Kaunas, Lithuania) 2006;43:199–207.
[33] Wahba WM, Don HF, Craig DB. Post-operative epidural analgesia: effects on lung volumes. Can Anaesth Soc J 1975;22:519–27.
[34] Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. Br J Surg 1985;72:495–8.
[35] Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC *et al*. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86:598–612.
[36] Licker M, de Perrot M, Spiliopoulos A, Robert J, Diaper J, Chevalley C *et al*. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003;97:1558–65.
[37] Licker M, Spiliopoulos A, Frey JG, Robert J, Hohn L, de Perrot M *et al*. Risk factors for early mortality and major complications following pneumonectomy for non-small cell carcinoma of the lung. Chest 2002;121:1890–7.
[38] Boisseau N, Rabary O, Padovani B, Staccini P, Mouroux J, Grimaud D *et al*. Improvement of 'dynamic analgesia' does not decrease atelectasis after thoracotomy. Br J Anaesth 2001;87:564–9.
[39] Gracey DR, Divertie MB, Didier EP. Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease: a prospective study. Chest 1979;76:123–9.
[40] Thomas JA, McIntosh JM. Are incentive spirometry, intermittent positive pressure breathing, and deep breathing exercises effective in the prevention of postoperative pulmonary complications after upper abdominal surgery? A systematic overview and meta-analysis. Phys Ther 1994;74: 3–10; discussion 10–16.
[41] Popping DM, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P *et al*. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Ann Surg 2014;259:1056–67.
[42] Polaner DM, Kimball WR, Fratacci MD, Wain JC, Zapol WM. Thoracic epidural anesthesia increases diaphragmatic shortening after thoracotomy in the awake lamb. Anesthesiology 1993;79:808–16.
[43] Azad SC, Groh J, Beyer A, Schneck D, Dreher E, Peter K. [Continuous peridural analgesia vs patient-controlled intravenous analgesia for pain therapy after thoracotomy]. Anaesthesist 2000;49:9–17.
[44] Peeters-Asdourian C, Gupta S. Choices in pain management following thoracotomy. Chest 1999;115(5 Suppl): 122s–4s.
[45] Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. Anesth Analg 2010;111:120–8.
[46] Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator-induced diaphragm dysfunction: cause and effect. Am J Physiol Regul Integr Comp Physiol 2013;305:R464–77.
[47] Drake-Brockman TF, Ramgolam A, Zhang G, Hall GL, von Ungern-Sternberg BS. The effect of endotracheal tubes versus laryngeal mask airways on perioperative respiratory adverse events in infants: a randomised controlled trial. Lancet (London, England) 2017;389:701–8.
[48] Aitkenhead AR. Anaesthesia and the gastro-intestinal system. Eur J Anaesthesiol 1988;5:73–112.
[49] Yukioka H, Tanaka M, Fujimori M. Recovery of bowel motility after high dose fentanyl or morphine anaesthesia for cardiac surgery. Anaesthesia 1990;45:353–6.
[50] Steinbrook RA. Epidural anesthesia and gastrointestinal motility. Anesth Analg 1998;86:837–44.
[51] Pompeo E. Awake thoracic surgery–is it worth the trouble? Semin Thorac Cardiovasc Surg 2012;24:106–14.
[52] Gibson P. Spinal cord damage following thoracic epidural anaesthesia. Anaesth Intensive Care 2004;32:596–7; author reply 597.
[53] Parker BM. Anesthetics and anesthesia techniques: impacts on perioperative management and postoperative outcomes. Cleve Clin J Med 2006;73(Suppl 1):S13–17.
[54] Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995;42:891–903.
[55] Crumley S, Schraag S. The role of local anaesthetic techniques in ERAS protocols for thoracic surgery. J Thorac Dis 2018;10:1998–2004.
[56] Park SY, Chun HR, Kim MG, Lee SJ, Kim SH, Ok SY *et al*. Transient Horner's syndrome following thoracic epidural anesthesia for mastectomy: a prospective observational study. Can J Anesth/J Can Anesth 2015;62:252–7.
[57] Kiss G, Castillo M. Non-intubated anesthesia in thoracic surgery-technical issues. Ann Transl Med 2015;3:109.
[58] Hung MH, Chan KC, Liu YJ, Hsu HH, Chen KC, Cheng YJ *et al*. Nonintubated thoracoscopic lobectomy for lung cancer using epidural anesthesia and intercostal blockade: a retrospective cohort study of 238 cases. Medicine (Baltimore) 2015;94:e727.
[59] Rivedal DD, Nayar HS, Israel JS, Leverson G, Schulz AJ, Chambers T *et al*. Paravertebral block associated with decreased opioid use and less nausea and vomiting after reduction mammaplasty. J Surg Res 2018;228: 307–13.
[60] Liang H, Liu J, Wu S, Zhang Y, Liu H, Yang H *et al*. Non-intubated spontaneous ventilation offers better short term outcome for mediastinal tumor surgery. Ann Thorac Surg 2019;108:1045–51.