

Peer review file

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Reviewer A

Comment 1: Were the two researchers co-authors? PI, lead author and how was that decided? Did one author have more experience dealing with Cochrane database analysis than the other? As it is generally difficult for thoracic surgeons to run these tests and statistical models.

Reply 1:

Dear Professor:

The "two researchers" mentioned in the paper are the first and second authors of the paper. Since we had doubts about the safety and efficacy of NIVATS in clinical practice, we found out the direction of this study. Therefore, we specifically learned from professors in our medical school and accumulated experience in meta-analysis. Therefore, these two authors were responsible for specific data processing and statistics.

Changes in the text: none.

Comment 2: How much NIVATS is performed at your hospital?

Reply 2:

Dear Professor:

NIVATS has been applied in our hospital since 2018, including lobectomy, Segmentectomy, mediastinal tumor resection and pulmonary bullae resection, etc. So far, more than 30 cases of NIVATS have been applied in surgery. In order to explore whether NIVATS can benefit patients, we carried out this meta-analysis study, and we will carry out relevant clinical trials for further exploration in the future.

Changes in the text: none.

Comment 3: Is there a biased to NIVATS in your particular hospital and if so, the biased should be discussed as another limitation

Reply 3:

Dear Professor:

There is no bias against NIVATS in our hospital. Before the application of the technology, the anesthesiologist went with us to learn NIVATS technology from Professor He Jianxing of the First Affiliated Hospital of Guangzhou Medical University. This technology also passed the ethical review and new technology approval of our hospital. With the support of hospital leaders and anesthesiology department, we carried out NIVATS technology steadily. We discussed the bias in the industry.

Changes in the text: line 364-373 on page 25

Comment 4: Another limitation in reviewing some of your studies that were looked at was the extreme heterogeneity and wide array of reporting, making it very difficult to determine a firm conclusion on whether NIVATS is actually worth pursuing

Reply 4:

Dear Professor:

The author tried to solve this problem by using subgroup analysis, but the heterogeneity of each subgroup was still high. Therefore, we will seriously consider your suggestions and adopt a more prudent way to summarize the conclusions.

In addition, there are numerous studies on NIVATS, many hospitals are trying to apply the technology, and some published studies have confirmed its advantages in rapid recovery. More clinical studies are needed to confirm whether the technology actually benefits patients, and mature and uniform technical standards are being developed. The author believes that the development of each new technology is accompanied by controversy. Just as thoracoscopy was just introduced into China many years ago, the controversy lasted for a long time, but now it has finally proved that the advantages of thoracoscopy in minimally invasive aspects are huge, and it has become the mainstream now. As an emerging technology, NIVATS is gradually entering the field of vision, and now it is more necessary to explore and follow up evidence-based evidence to solve the disputes about this technology. Therefore, meta-analysis of this technology is very necessary.

Changes in the text: line 276-289 on page 21

Comment 5: I think overall for the conclusion section: this needs to be changed and lessened to a far less aggressive stance

Meaning I think in its current state NIVATS is very seldom used and benefits are still questionable. With that being said I think it can be helpful for sick patients that cannot tolerate GETA, but for most of our patients they do fine with gETA and VATS surgery, thus I would also like the authors to discuss their thoughts on which patients might benefit from NIVATS or if they are recommending all patients to undergo NIVATS which I think is highly unlikely.

I think it would be good for pleural biopsies and pleuroscopy type procedures but even our VATS patients do well with these procedure Vats.

Can the authors also describe the surgical field satisfaction score in more detail?

Reply 5:

Dear Professor:

1. Currently, patients receiving NIVATS need to meet more stringent indications than GETA, which include :(1) simple surgical procedure and short time;(2) Less airway secretion;(3) Patients with respiratory diseases, such as tuberculosis, COPD, sleep apnea, etc. are clinically confirmed to have no medical history of circulatory diseases, such as congenital heart disease and coronary heart disease;(4) the cardiopulmonary function, ASA class I ~ II;(5) No contraindications related to other epidural anesthesia and other anesthesia methods. These patients will receive GETA before, but now we will recommend NIVATS to these patients, because according to the current domestic and foreign studies and our experience, they will have a shorter recovery time and will benefit from NIVATS.

Changes in the text: line 366-368 on page 25

2. In addition, many special patients are difficult airway patients who cannot bear double-lumen endotracheal intubation, such as patients with stiff neck (cervical trauma requiring immobilization or severe cervical spondylosis requiring elective surgery, etc.). These patients are difficult to operate under endotracheal intubation. There was once an elderly male patient in our department who had a history of cervical spine surgery and had stiff neck. Conventional double-lumen endotracheal intubation was inserted into the endotracheal sac and the endotracheal sac was ruptured, but the single-lumen endotracheal balloon was still ruptured, and 5 cannula

were lost. The patient recovered well after the application of autonomic respiration lobectomy plus lymph node dissection. At that time, if we had chosen tracheotomy, we would still be inoperable if the cuff was broken. So, for some patients who are not suitable for endotracheal intubation, NIVATS offers an alternative.

Changes in the text: line 368-373 on page 25

3. In terms of the satisfaction score of the operative field, the current applied satisfaction score of the operative field is as follows: 1 point, complete lung collapse, well exposed operative field; 2 points: Lung collapse is normal, the surgical field of vision is relatively clear, but there is no need to interrupt the operation; 3 points: poor surgical field exposure, unsatisfactory lung collapse, repeated need to interrupt surgery; 4 points: poor exposure of surgical field, failure to complete the operation, transfer to intubation surgery. Because in the three studies that reported the operative field score, the patients' operative field score was mostly 1 (complete lung collapsed, the operative field was well exposed), this paper studied the patients with this part of the score to explore whether NIVATS and GETA had fairly good operative field.

Changes in the text: line 216-222 on page 17

It is a great honor to communicate with you. Your in-depth and detailed suggestions have benefited us a lot.

Reviewer B

Comment 1: One of the major concerns related to non-intubated VATS is the conversion to the intubated VATS during the surgery. The data for the conversion rates should be analyzed for the 14 RCTs.

Reply 1:

Dear Professor:

We quite agree with the professor's point of view, but the number of reported transfer cannulation is too small to carry out the combined analysis, so we discuss and review this indicator according to the existing research. Relevant texts have been added in the text, and we also expect more studies to report this important indicator in the future.

Changes in the text: line 374-381 on page 25

Comment 2: The data for the long-term outcomes (survivals or long term adverse effects) should be mentioned.

Reply 2:

Dear Professor:

As for the survival indicator, we quite agree with the professor's opinion. Since NIVATS is still in the preliminary stage of development, the study on long-term survival outcome is under way, and we also expect more studies to report this important indicator, and we will also actively discuss and follow up. The relevant text has been added to the body discussion section.

Changes in the text: line 381-384 on page 25-26

Comment 3: The safety and efficacy data of non-intubated VATS are still insufficient for lung cancer patients especially for those who need lobectomy or segmentectomy. This should be emphasized.

Reply 3:

Dear Professor:

We will emphasize this point in the text.

Changes in the text: line 361-363 on page 25

Comment 4: Figure 7 is not necessary. We can see the data in Figures 4 or 5.

Reply 4:

Dear Professor:

We have deleted the Figure 7.

Changes in the text: line 186-188 on page 14

It is a great honor to communicate with you. Your in-depth and detailed suggestions have benefited us a lot.

Reviewer D

Comment 1: While this work is not possible without an investment of many working hours, I have still troubles to realize what new knowledge it is aimed to depict. Is NIVATS feasible – sure it is, it has already been showed in many valuable

publications for particular indications. Is it safe – according to available studies it should be, again for certain indications most probably, however, for some others valuable body of evidence is missing (anatomical resections).

The authors have decided to include 14 RCT, which represents more than necessary sample size for meaningful analysis. However, those studies do not represent one particular surgical indication, but rather a heterogeneous group consisting of minor surgical procedures like pleurodesis or hyperhidrosis, two pneumothoraces, one bulla resection, one emphysema surgery, one chest wall surgery (Nuss procedure), one pulmonary nodule resection (presumably wedge) and six papers with variety indications, anatomical resection being almost completely ignored.

Reply 1:

Dear Professor:

In the author's opinion, NIVATS is more likely to be regarded as a new attempt of anesthesia based on the advancement of anesthesia management technology than as an original "exclusive surgical procedure" for some patients who fit the indications. Previously, we left the back to the endotracheal tube, but now we are equipped with a laryngeal mask airway, epidural anesthesia, thoracic paraphernalia block, intercostal nerve block and other weapons to protect the patient during the operation. With the development of technology and the broadening of indications for NIVATS, Wu and his colleagues (1) evaluated the feasibility of lobotomy in elderly patients (65-87 years old), showing comparable safety compared with the control group and opening up the possibility of NIVATS in elderly patients.

However, in the development process, risks and challenges should not be ignored. The biggest risk is the poor safety of respiratory tract maintenance, and the shortcomings of this technique are the face of transfer intubation at any time, intraoperative hypoxemia and hypercapnia, mediastinal swing, cough reflex caused by pulling the hilum, etc.

Therefore, in this case, on the one hand, more and more in-depth studies are needed to confirm its feasibility and broaden its indications; On the other hand, more in-depth and extensive research is needed to explore measures to face these risks and ensure their safety. So, NIVATS as emerging technology is slowly entered the view of the industry, the definition of the indications of hypoxemia and hypercapnia and mediastinum swing and cough reflex, risk of operation field, the influence of the

postoperative complications and other issues are still controversial and prejudice, now more need to evidence-based evidence to explore and follow up, to deal with disputes, so the author thinks that meta analysis of the technology is very necessary.

As for anatomical resections, as NIVATS is still in the preliminary stage of development, there are not enough research data for meta-analysis of anatomical resections. We also look forward to more NIVATS studies on anatomical resections in the future, which will be discussed in the paper.

(1) Wu CY, Chen JS, Lin YS, et al. Feasibility and safety of nonintubated thoracoscopic lobectomy for geriatric lung cancer patients. *Ann Thorac Surg* 2013;95:405-11

Changes in the text: line 361-373 on page 25

Comment 2: Primary outcome was defined to be the length of hospital stay. It is to my belief related to this outcome in particularly that one definite conclusion cannot easily be made due to heterogeneity of the study groups and especially surgical indications. The authors even more decided to remove the subgroup with anatomical resections, arguably the only where the feasibility and safety studies still haven't sufficiently been performed. On top of it, they failed to address this detail in conclusion, claiming simply, that NIVATS seemed to have shorter LOS than VATS. In Figure 3 they are mentioning operation size – now, it would be useful to define it for once priory. While one included study, which had shown shorter LOS cannot be approached or analyzed as on Chinese, two further (Pompeo 2004 and Pompeo 2007) had a day difference in LOS (2 vs. 3 days) with 60 and 43 patients respectively. Moreover, LOS was not the primary goal of the later one.

Reply 2:

Dear Professor:

The author tried to use subgroup analysis to solve this problem, but the heterogeneity of each subgroup was still high. Therefore, we will carefully consider your suggestions and adopt a more prudent way to conclude the conclusion.

Changes in the text: line 276-284 on page 21

Comment 3: Also it seems to be more logical to analyze subgroups according to surgical procedures performed. There have been six variety studies which have been analyzed on operation time as if they represent a dedicated surgical indication. I

would like to see comparison of patients undergoing the same surgical procedure and conclusions upon the results.

Reply 3:

Dear Professor:

Due to the different surgical approaches reported in each study, a subgroup analysis was attempted, but only three studies with bullous lung resection could be combined (Figure 7), ($P = 0.12$, $I^2 = 53\%$) (MD: -1.57; 95% CI, -5.12 to 1.98; $P = 0.12$).

Changes in the text: line 286-289 on page XX

Comment 4: I think that surgical field satisfaction needs further clarification, despite this term was not introduced but analyzed from the authors.

Reply 4:

Dear Professor:

In terms of the satisfaction score of the operative field, the current applied satisfaction score of the operative field is as follows: 1 point, complete lung collapse, well exposed operative field; 2 points: Lung collapse is normal, the surgical field of vision is relatively clear, but there is no need to interrupt the operation; 3 points: poor surgical field exposure, unsatisfactory lung collapse, repeated need to interrupt surgery; 4 points: poor exposure of surgical field, failure to complete the operation, transfer to intubation surgery. In the three studies that reported surgical field score, the patients' surgical field score was mostly 1 point (complete lung collapsed, the operative field was well exposed), and no cases with poor operative field condition were reported. Therefore, this paper studied the patients with this part of the score to explore whether NIVATS and GETA had fairly good operative field.

Changes in the text: line 216-222 on page 17

Comment 5: On the page 18, line 203 authors claim the VAS scores in the NIVATS group to be higher than those in the control group. Later, in conclusion they claim the opposite.

Reply 5:

Dear Professor:

Thank you very much for your comments. We have checked our article and found that this is indeed a wording error. Our study showed that the NIVATS group had a lower

VAS score than the VAS group, indicating less postoperative pain in the NIVATS group, and the conclusion should be changed to "The NIVATS group had a lower VAS score than the VAS group."

Changes in the text: line 232 on page 17

Comment 6: I am keen on to find out more about the complications: what were there (intra/postOP)? It is also interesting to see the explanations of the authors about statistical significance in incidence of complications between to arms favoring NIVATS group while having only 8 out of 14 RCT studies analyzed and only two of them had showed favoring differences while other six had not. Respiratory complications in particularly were again more often in control group while only one study (Liu) out of eight involved in this statistic had showed it. The same is with the air leak (Pompeo 2012), again 1/8.

Intubated related complications are another story: authors included only three out of 14 paper, two of them (Chen and Wang) having astonishing 32 out of 83 complications at intubation. Those anesthesiologists need to undergo some serious schooling. No comments from authors there either. A hoarseness rate and gastrointestinal reaction need further clarifications from authors in discussion.

Reply 6:

Dear Professor:

Complications: intubation related complications (pharyngeal discomfort, hoarseness), respiratory complications (pneumothorax, atelectasis, infection), circulatory complications (atrial fibrillation and other arrhythmias, myocardial infarction, etc.), digestive complications (nausea, vomiting, diarrhea).

Your in-depth and detailed suggestions have benefited us a lot and helped us find some new contents worthy of attention. We have taken your suggestions into consideration and added new contents in the discussion section. Thank you again for your generous comments. Finally, it is my great honor to communicate and discuss with you, and your suggestions are of great help to our improvement.

Changes in the text: line 322-329 on page 23