Peer review file

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Reviewer A

Major points

Comment 1: This meta-analysis evaluated only six factors including operative time, blood loss, numbers of lymph node, postoperative hospital stay, chest drainage time, postoperative complication rate, and overall survival. However, the choice of procedure is usually depended on the patient's backgrounds including, comorbidities, respiratory function, tumor size, and lymph node status as well as disease free survival. Couldn't these important factors have been added to the consideration?

Reply 1:

We appreciate your constructive comments and we agree with you that the baseline characteristics of patients are also important predictors for perioperative outcomes and oncological results of patients with NSCLC. Therefore, in the revision, we have provided descriptions of patient's backgrounds including age, sex, BMI, smoking history, FEV1%, tumor location, histological type, pathological T stage and pathological N stage between two surgical approaches. As shown in Table 2, no significant difference was observed in baseline characteristics between thoracoscopic and thoracotomy sleeve lobectomy. Unfortunately, the data of comorbidity and long-term disease-free survival were only obtainable in three articles, which limited the implementation of meta-analysis based on these two factors.

Changes in the text:

Line 165-169:

Baseline Characteristics

As displayed in Table 2, baseline characteristics of patients including age, sex, body mass index (BMI), smoking history, FEV1%, tumor location, pathological T stage and pathological N stage were all similar between the thoracoscopic and thoracotomy groups.

Table 2 Baseline characteristics between thoracoscopic and thoracotomy sleeve lobectomy

Variables	Number of publications	Test for overall effect		Test for heterogeneity	
		Thoracoscopy vs. Thoracotomy	p value	I^2	p value

Age (SMD [95%CI])	5	-0.01 (-0.19, 0.16)	0.868	0%	0.934
Sex (Male) (RR [95%CI])	6	1.00 (0.88, 1.13)	0.952	0%	1.000
BMI (SMD [95%CI])	5	0.04 (-0.13, 0.21)	0.633	0%	0.971
FEV1% (SMD [95%CI])	4	-0.16 (-0.37, 0.05)	0.145	25.50%	0.259
Smoking (Ever) (RR [95%CI])	6	0.97 (0.83, 1.13)	0.666	0%	0.617
Histological type (SCC) (RR [95%CI])	6	1.00 (0.87, 1.15)	0.981	0%	1.000
Location (Left) (RR [95%CI])	6	1.08 (0.89, 1.30)	0.450	0%	0.928
pT1 Stage (RR [95%CI])	3	1.09 (0.68, 1.76)	0.713	0%	0.497
pT2 Stage (RR [95%CI])	3	1.03 (0.86, 1.23)	0.772	0%	0.811
pT3 Stage (RR [95%CI])	3	1.11 (0.40, 3.08)	0.839	68%	0.044
pT4 Stage (RR [95%CI])	2	0.61 (0.21, 1.76)	0.361	0%	0.489
pN0 Stage (RR [95%CI])	4	1.04 (0.85, 1.27)	0.724	0%	0.976
pN1 Stage (RR [95%CI])	4	0.93 (0.63, 1.37)	0.712	0%	0.518
pN2 Stage (RR [95%CI])	4	0.95 (0.69, 1.32)	0.775	0%	0.775

BMI, body mass index; SCC, squamous cell carcinoma; Note: For propensity matched studies, only cases after matching were included

Comment 2: There is a question of whether we can draw conclusions from a meta-analysis of only six papers from only one nation. The fact that nonsignificant studies and studies with negative findings will be less likely to be published. It is not possible to determine whether the results of this study can be replicated for different surgeons, institutions or countries.

Reply 2:

We thank the reviewer for raising this significant question and we have acknowledged the limitation of our study in the number of included publications. In this meta-analysis, we only included six papers from a single nation, which may weaken the generalization and robustness of our conclusions. However, this limitation may partly arise from some objective conditions. Firstly, thoracoscopic sleeve lobectomy is a technically demanding procedure and is only performed in hands of experienced surgeons from large medical centers, which contributes to limited literatures about this surgical procedure. Besides, due to the large patient population of NSCLC in China, medical centers from China can accumulate more experience than that from other countries, several centers in China have routinely performed thoracoscopic sleeve lobectomy. Therefore, most publications comparing thoracoscopic versus thoracotomy were reported by Chinese centers. Admittedly, as you comment, we cannot determine whether the results of this study can be replicated for different surgeons, institutions or countries. But at least this meta-analysis has achieved significant results in operative time and overall survival, which are new findings different from existing studies. As such, we believe our results have reference value for the following studies investigating the efficacy of thoracoscopic sleeve lobectomy. Finally, we also expect that international large-scale trials in future could confirm our findings.

Comment 3: How many cases do you think you need to gain experience to learn this difficult surgery? Because the cases of sleeve lobectomy itself are decreasing along with decreasing of centrally located squamous carcinoma. In addition, how many surgeons are involved in these papers? Is this a special surgery for just one surgeon?

Reply 3:

Thank you for this important comment. We think your question on learning curve of thoracoscopic lobectomy is really worth further exploring. The learning curve of thoracoscopic sleeve lobectomy is of great clinical significance, which will provide instructions for thoracic surgeons to learn and master this difficult surgical procedure. But unfortunately, considering that our study is a meta-analysis based on existing publications and there is no study investigating the learning curve of thoracoscopic sleeve lobectomy, we cannot know how many cases a thoracic surgeon needs to gain experience to learn this difficult surgery. Even so, this question is very interesting and valuable. Actually, we are conducting another original study to investigate the learning curve of thoracoscopic sleeve lobectomy based on data in our center, but the preliminary results have not been drawn. Therefore, we are sorry that we cannot clearly answer this question in here. In addition, among six included articles in this meta-analysis, only the study by Xie et al. (1) provided the information about surgeon distribution, in their report, total eight thoracic surgeons are involved (Table-response 1).

Table-response 1

	All patient (n=363)			Matched cohort (n=188)		
	Thoracotomy (n=251)	VATS (n=112)	p	Thoracotomy (n=116)	VATS (n=72)	p
Surgeons, n (%)			<0.01			0.72
A	41 (16.3)	11 (9.8)		21 (18.1)	9 (12.5)	
B	20 (8.0)	8 (7.1)		11 (9.5)	8 (11.1)	
C	43 (17.1)	8 (7.1)		15 (12.9)	8 (11.1)	
D	58 (23.1)	12 (10.7)		22 (19)	12 (16.7)	
E	23 (9.2)	55 (49.1)		23 (19.8)	23 (31.9)	
F	20 (8.0)	2 (1.8)		3 (2.6)	2 (2.8)	
G	19 (7.6)	4 (3.6)		10 (8.6)	4 (5.6)	
H	27 (10.8)	12 (10.7)		11 (9.5)	6 (8.3)	

Comment 4: How can we select the procedure? For which cases should VATS be performed? Conversely, which cases should be done with thoracotomy? Please state your thoughts.

Reply 4:

Thank you for this significant question. From our experience, decisions to perform thoracotomy versus VATS sleeve are made by the operating surgeons. Generally, surgeons select the surgical approach based on conditions of patients and characteristics of tumors. If certain risk factors for thoracoscopic surgery (including preoperative induction therapy, T4 tumor, fibrocalcified lymph nodes, pleural adhesions, ipsilateral reoperation, vascular invasion, etc) are identified before surgery, surgeons may tend to adopt thoracotomy, otherwise thoracoscopic surgery may be attempted. However, there is no mandatory criterion for surgical approach selection, it mainly decided by surgeons based on resectability of tumors and surgical difficulty after comprehensive preoperative evaluation.

Comment 5: These six references include complete, uniportal and robotic surgery among “thoracoscopic”, how would you explain the differences between them?

Reply 5:

We appreciate the reviewer for this significant comment. With the development of thoracoscopic technique in the past decades, thoracoscopic surgery has experienced from multiportal VTAS, then uniportal VATS, to robotic surgery. Uniportal VTAS has the advantage of less trauma and rapid recovery over multiportal VTAS (2,3). Despite the difference between these two surgical approaches, both multiportal and uniportal VATS have been demonstrated to have significantly better perioperative outcomes and equivalent oncological results compared to conventional thoracotomy in patients with NSCLC (4,5). Therefore, we took these two surgical procedures as a whole in analyses, which is similar to many other studies (6-8). Regarding robotic surgery, two large-sample meta-analysis studies have indicated that robotic surgery achieves similar operative outcomes to VATS, and no matter robotic surgery or VATS yielded superior outcomes than conventional thoracotomy (6-8). Besides, the existing studies comparing VATS versus thoracotomy for sleeve lobectomy are very limited. As such, theses three approaches were all taken as the thoracoscopic group when compared to conventional thoracotomy. In addition, in the revised manuscript, we have clarified this issue in the beginning.

Even so, the potential bias resulting from the differences among these three surgical approaches are inevitable, which may weaken the robustness of this study, and in this revision, we have additionally discussed this point in the limitation section.

Changes in the text:

Line 130-132: Video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) cases were integrated into the thoracoscopic group for further comparison with the thoracotomy group.

Line 332-336: Additionally, limited by the number of studies investigating thoracoscopic sleeve lobectomy, the uniportal VATS, multiportal VATS and RATS cases were analyzed as a whole when compared with the thoracotomy group and subgroup analyses based on surgical approaches could not be performed, so the potential bias resulting from the differences among these three surgical approaches are inevitable.

Minor points

Comment 1: Some papers seem to include an average observation period of less than 5 years. Can we conclude from this that the survival rate is equivalent to that of thoracotomy?

Reply 1:

Thank you for this important comment. In the study of Gu et al. (9), the median follow-up time was only 20 months, which may not support the conclusion that the long-term survival rate of thoracoscopic surgery is equivalent to that of thoracotomy. Therefore, in the revision, we removed this publication from the survival analysis. and as shown in Figure 8, the thoracoscopic group achieved non-inferior oncological results compared to the thoracotomy group and no evident publication bias were identified among included studies.

Changes in the text:

Figure 9. Meta-analysis: the overall survival for thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included

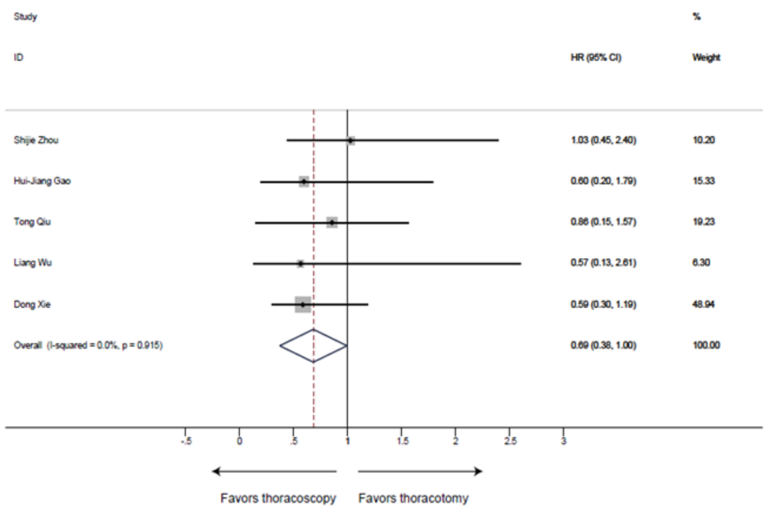
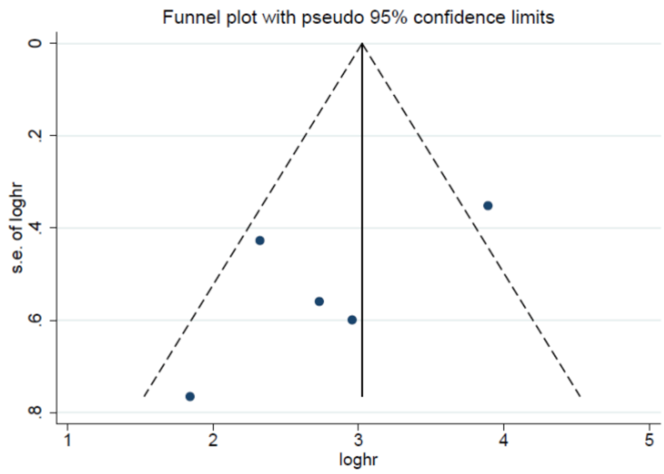


Figure 10. The funnel plot and publication bias tests for the overall survival of thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included



Tests for Publication Bias

Begg's Test: p=0.806

Egger's Test: p=0.193

Comment 2: Do you have any data on conversion rate?

Reply 2:

We appreciate your important question. The conversion rate of each included study is listed in the following table. In the revision, we have provided data of conversion rate in the baseline characteristics table.

Table-response 2

Study	Conversion
Shijie Zhou, 2015	0%
Chang Gu, 2018	1.7%
Hui-Jiang Gao, 2019	5.6%
Tong Qiu, 2019	2.9%
Liang Wu, 2019	Not Given
Dong Xie, 2020	4.5%

Changes in the text:

Table 1 Baseline characteristics of included studies

Author, year	Country	Study type	Treatment	Conversion rate	Number of patients	Mean age, year	Male/Female	Pathological stage		
								I	II	III
Shijie Zhou, 2015	China	Cohort	Thoracoscopy	0%	10	60.5	9/1	6	2	2
			Thoracotomy		41	62.5	35/6	18	10	13
Chang Gu, 2018	China	Cohort	Thoracoscopy	1.7%	17	62.0	17/0	6	5	6
			Thoracotomy		86	61.1	80/6	36	29	21
Hui-Jiang Gao, 2019	China	Cohort	Thoracoscopy	5.6%	54	60.7	44/10	23	19	12
			Thoracotomy		94	60.4	87/7	20	35	39
Tong Qiu, 2019	China	Cohort	Thoracoscopy	2.9%	122	60.4	108/14	NG	NG	NG
			Thoracotomy		66	61.1	62/4	NG	NG	NG
Liang Wu, 2019	China	Cohort	Thoracoscopy	NG	21	62.0	19/2	8	4	9
			Thoracotomy		21	61.0	19/2	7	6	8
Dong Xie, 2020	China	Cohort	Thoracoscopy	4.5%	112	62.7	91/21	48	35	29
			Thoracotomy		251	62.1	234/17	104	72	75

Quality assessment of included studies was performed using the modified Newcastle–Ottawa Scale (NOS); NG, not given.

Comment 3: Line 226: several series of stusies reported → studies, I think this is typo.

Comment 4: Line 227: a serious of case reports→ series, I think this is typo.

Reply 3 and Reply 4 :

We apologize for these terrible spelling mistakes. In the revision, the typos have been corrected accordingly. In addition, we have carefully checked and corrected the spelling and syntax mistakes and asked a native English-speaking expert to review the wording of this article.

Changes in the text:

Line 241-242: Subsequently, several series of studies reported their experience in sleeve lobectomy through video-assisted mini-thoracotomy.

Line 244-245: Thereafter, a series of case reports described complete VATS sleeve resection via three or four ports.

References

1. Xie D, Deng J, Gonzalez-Rivas D, et al. Comparison of Video-assisted Thoracoscopic Surgery with Thoracotomy in Bronchial Sleeve Lobectomy for Centrally Located Non-Small Cell Lung Cancer. The Journal of Thoracic and Cardiovascular Surgery 2020.

2. Abouarab AA, Rahouma M, Kamel M, et al. Single Versus Multi-Incisional Video-Assisted Thoracic Surgery: A Systematic Review and Meta-analysis. J Laparoendosc Adv Surg Tech A 2018;28:174-85.

3. Harris CG, James RS, Tian DH, et al. Systematic review and meta-analysis of uniportal versus multiportal video-assisted thoracoscopic lobectomy for lung cancer. Ann Cardiothorac Surg 2016;5:76-84.

4. Boffa DJ, Dhamija A, Kosinski AS, et al. Fewer complications result from a video-assisted approach to anatomic resection of clinical stage I lung cancer. J Thorac Cardiovasc Surg 2014;148:637-43.

5. Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg 2009;138:11-8.

6. Ye X, Xie L, Chen G, et al. Robotic thoracic surgery versus video-assisted thoracic surgery for lung cancer: a meta-analysis. Interact Cardiovasc Thorac Surg 2015;21:409-14.

7. Kent M, Wang T, Whyte R, et al. Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database. Ann Thorac Surg 2014;97:236-42; discussion 42-4.

8. Emmert A, Straube C, Buentzel J, et al. Robotic versus thoracoscopic lung resection: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e7633.

9. Gu C, Pan X, Chen Y, et al. Short-term and mid-term survival in bronchial sleeve resection by robotic system versus thoracotomy for centrally located lung cancer. Eur J Cardiothorac Surg 2018;53:648-55.

Reviewer B

Comment 1: Abstract:

Was the study registered? According to the PRISMA check-list the registration number should be presented.

Reply 1:

Thank you for this important comment and we agree with you that registration is important for a meta-analysis. Our study was conducted according to the standard PRISMA check-list. This meta-analysis has been submitted for registration on PROSPERO and the ID is 200320. However, the registration is still in the process of reviewing. Once the registration was approved, we will provide the information in our manuscript.

Comment 2: Introduction:

lines 82-3. The authors state: "Centrally located non-small-cell lung cancer (NSCLC) is an intractable type of lung neoplasms". It is true that centrally located tumors depicted a difficult task for the surgeon because the need for pneumonectomy is always there. But these tumors are tractable. Please modify the sentence.

In my opinion, it is not necessary to add the PRISMA checklist not even as supplementary table because the reference is already there. Therefore, the reader not familiar with the methodology can easily access it from the publication.

Reply 2:

We appreciate these constructive comments. We agree that centrally-located tumors depict a difficult task for surgeon but they are tractable. Therefore, in the revision, we have modified this sentence to "Centrally located non-small-cell lung cancer (NSCLC) is the second common type of lung neoplasms".

We thank you for the suggestions on the methodology of meta-analysis. In the revised manuscript, we have removed the PRISMA checklist from the supplementary material.

Changes in the text:

Line 82-83: Centrally located non-small-cell lung cancer (NSCLC) is the second common type of lung neoplasms, and curative intent surgery is the preferred therapeutic strategy.

Comment 3: Results:

There is a typo in line 191… “5 articles contained data of chest drainage time and demonstrated”. Please correct.

I would suggest adding an arrow and a little text saying favors thoracotomy as appropriated in every figure. It should help to better understand the results of the different figures.

Reply 3:

We apologized for this terrible mistake. In the revision, this sentence has been modified to “5 articles reported data of chest drainage time and our meta-analysis demonstrated patients receiving sleeve lobectomy via thoracoscopic have similar chest drainage time to those via thoracotomy”.

We think your suggestion is valuable for the improvement of the quality of our article. In the revision, we have added an arrow and a little text saying the results favor thoracotomy or thoracoscopic surgery.

Changes in the text:

Line 196-199: 5 articles reported data of chest drainage time and our meta-analysis demonstrated patients receiving sleeve lobectomy via thoracoscopic have similar chest drainage time to those via thoracotomy (SMD=-0.26, 95% CI, [-0.69, 0.17], $p=0.235$), with specific heterogeneity ($p<0.001$, $I^2 = 80.6\%$) (Figure 6).

Figure 2. Meta-analysis: the operation time for thoracoscopic and thoracotomy sleeve lobectomy

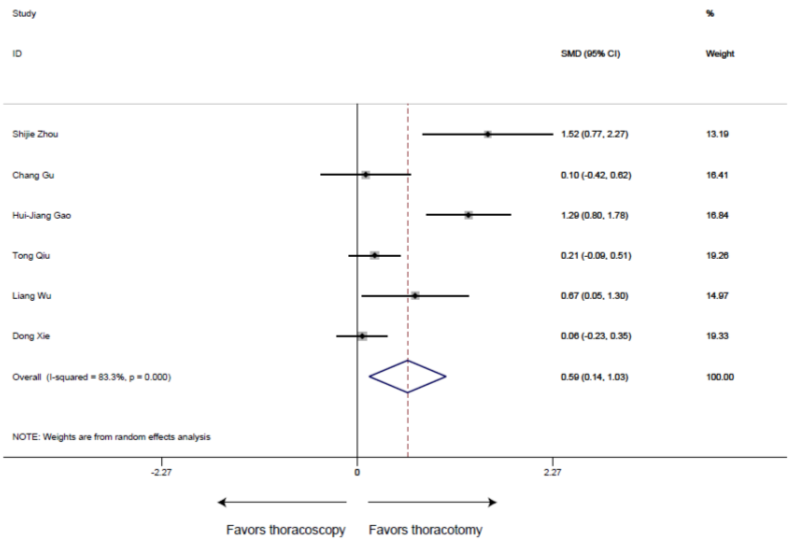


Figure 3. Meta-analysis: the blood loss for thoracoscopic and thoracotomy sleeve lobectomy

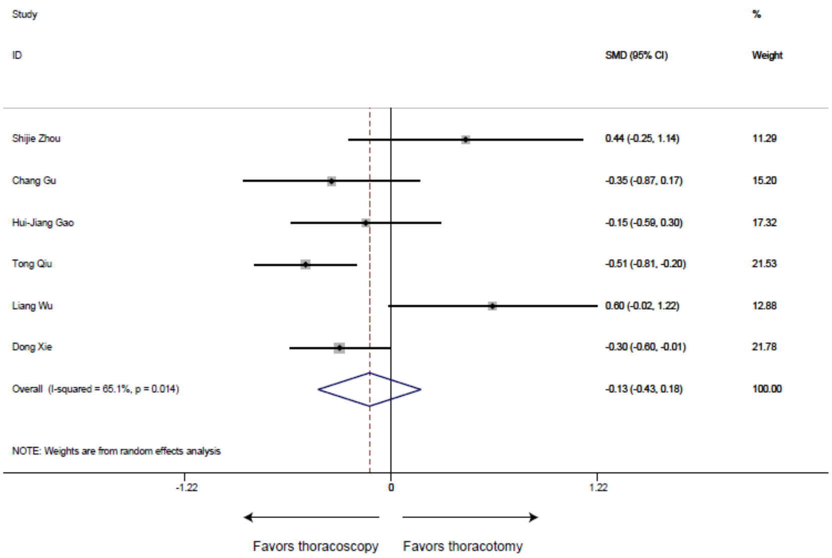


Figure 4. Meta-analysis: the number of resected lymph nodes for thoracoscopic and thoracotomy sleeve lobectomy

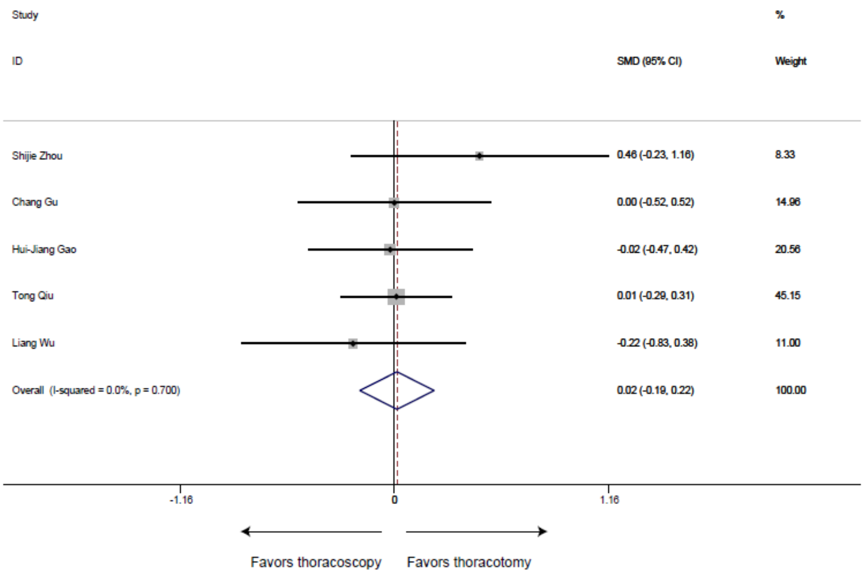


Figure 5. Meta-analysis: the postoperative hospital stay for thoracoscopic and thoracotomy sleeve lobectomy

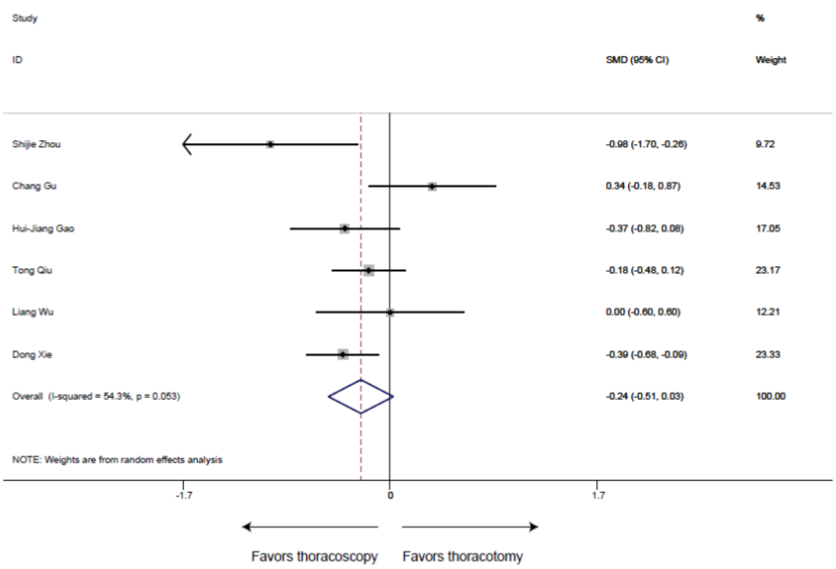


Figure 6. Meta-analysis: the chest drainage time for thoracoscopic and thoracotomy sleeve lobectomy

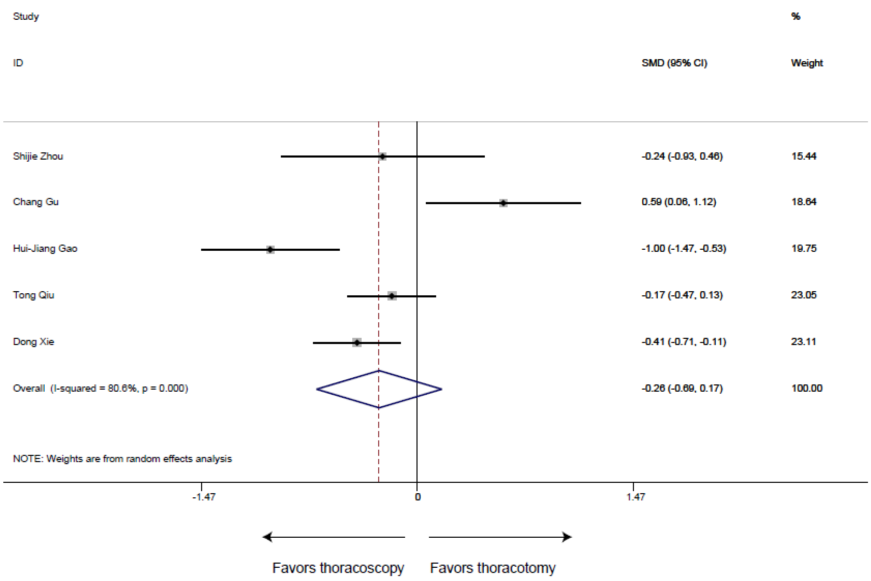


Figure 7. Meta-analysis: the postoperative complication rate for thoracoscopic and thoracotomy sleeve lobectomy

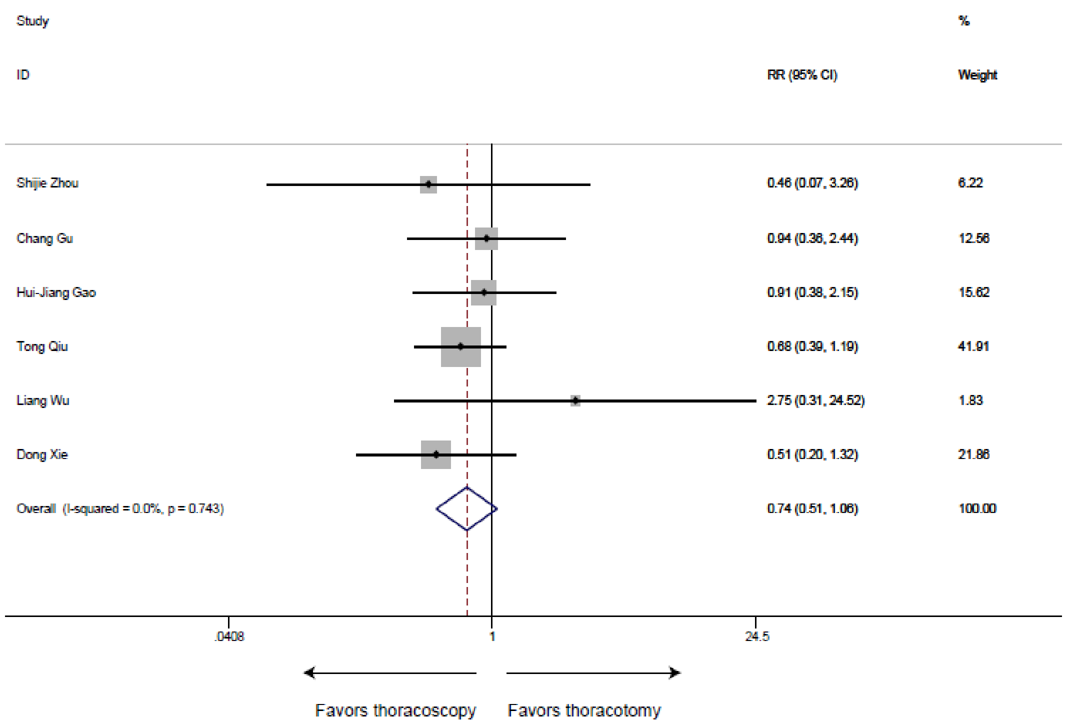


Figure 8. Meta-analysis: the 30-day (A) and 90-day (B) mortality rate for thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included

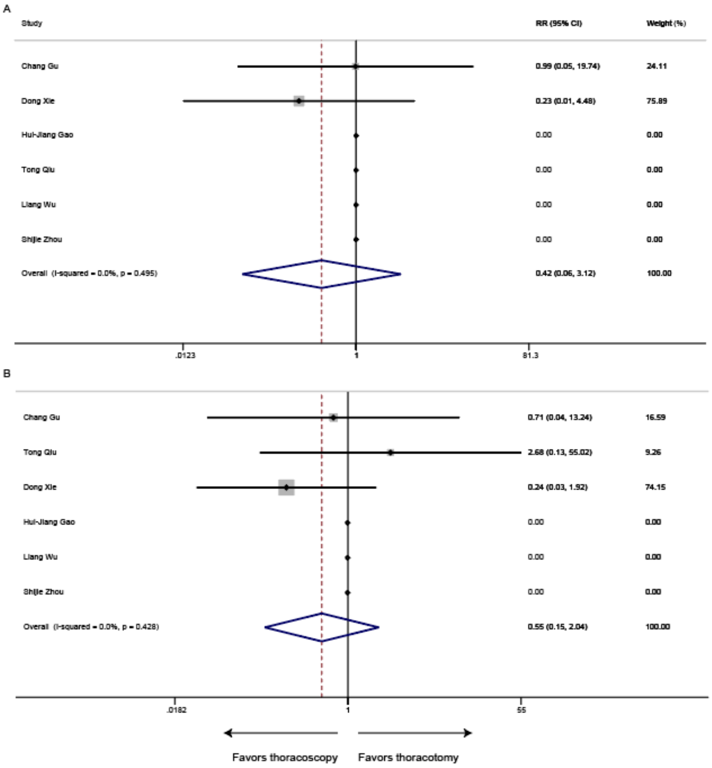
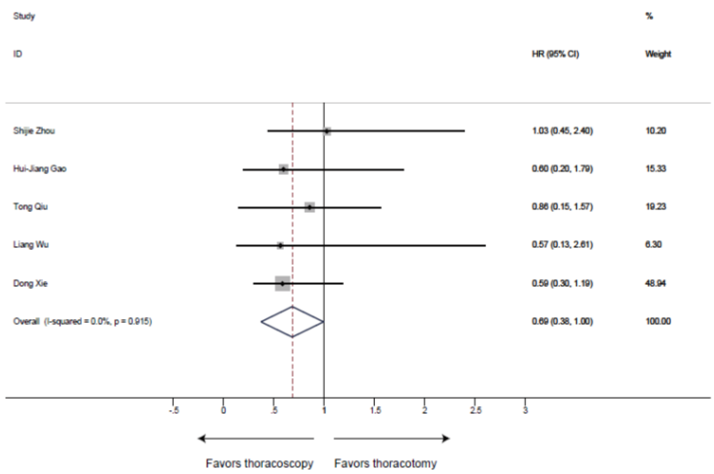


Figure 9. Meta-analysis: the overall survival for thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included



Comment 4: Discussion:

Although the rest of the manuscript has no typos or grammar errors. This section needs a review by a native-English speaker.

Lines 238-240. This is an interesting sentence when commenting on the first sleeve resection on non-intubated surgery of this type: “the patient got off bed on the first postoperative day and was discharged after 6 days of operation”. I would suggest remarking other possible relevant outcomes from the case-report because all patients after VATS/RATS or open approach should get out the bed on postoperative day 1 for securing better outcomes and 6 days is a standard LOS for a sleeve resection. On the other hand, one of the objectives of non-intubated surgery is exactly “fast” normality. Please, modify.

This is another interesting sentence (lines 302-304): “Additionally, our research revealed thoracoscopy sleeve lobectomy can offer a significant advantage on OS over thoracotomy sleeve lobectomy” however it did not as shown below. Please add a sound reason for this statement or delete it.

Reply 4:

We appreciate these important comments. We have acknowledged that we do not make reasonable descriptions of the results of non-intubated thoracoscopic sleeve lobectomy to indicate the advantage of non-intubated surgery in “fast” normality. After remarking other possible relevant outcomes from the case-report, we have modified the description for the results of non-intubated surgery in the revised manuscript.

According to the suggestion of another reviewer, we exclude the study of Gu et al. (1) in which the follow-up time was not long enough. In the revision, the overall survival of thoracoscopic sleeve lobectomy shows significant advantage over conventional thoracotomy ($p<0.001$, HR: 0.38-1.00) (figure 9). However, in the original results of all included studies, no significant difference was observed in OS between two groups, which might be the consequence of the limited sample size of thoracoscopic sleeve lobectomy. Therefore, we may not draw a radical conclusion, but at least the thoracoscopic did not compromise the survival outcomes to thoracotomy. And in the revision, we have added an explanation for this statement.

Changes in the text:

Line 278-288: In larger and more experienced centers, sleeve lobectomy via thoracoscopic surgery could confer superiority in perioperative outcomes over that by thoracotomy. Radical lymphadenectomy is of great importance in reducing the late recurrence risk after surgical resection of tumors. For all six included researches, there was no significant difference in performance of intraoperative lymph nodes dissection between thoracoscopy and thoracotomy groups.

In terms of postoperative outcomes, five included studies revealed no statistical difference in postoperative complication rate between the thoracoscopic and thoracotomy groups. Only one research proved lower complication rate after thoracoscopic sleeve resection.

Line 311-315: Additionally, as displayed in Figure 9, our research revealed thoracoscopy sleeve lobectomy can offer a significant advantage on OS over thoracotomy sleeve lobectomy ($p<0.001$, HR: 0.38-1.00). However, in the original results of all included studies, no significant difference was observed in OS between two groups, which might be the consequence of the limited sample size of thoracoscopic sleeve lobectomy.

Line 253-256: In this case, the operative time was 165 minutes, the patient did not require assisted ventilation after surgery, he could drink and eat without any restriction at 4 h postoperatively and became mobile at the first postoperative day. This patient was discharged after 6 days of operation and no complication was identified.

Comment 5: Other questions:

- It is surprising that data on mortality is missing. Is it possible to include a comment on this issue which I think is quite relevant?

Reply 5:

Thank you for this constructive suggestion. The mortality rate is an important indicator to evaluate the feasibility of a surgical procedure. In the revision, we have provided the results of mortality. As shown in Figure 8 and Figure S7, no significant difference was observed between two surgical approaches and no evident publication was identified.

Changes in the text:

Figure 8. Meta-analysis: the 30-day (A) and 90-day (B) mortality rate for thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included.

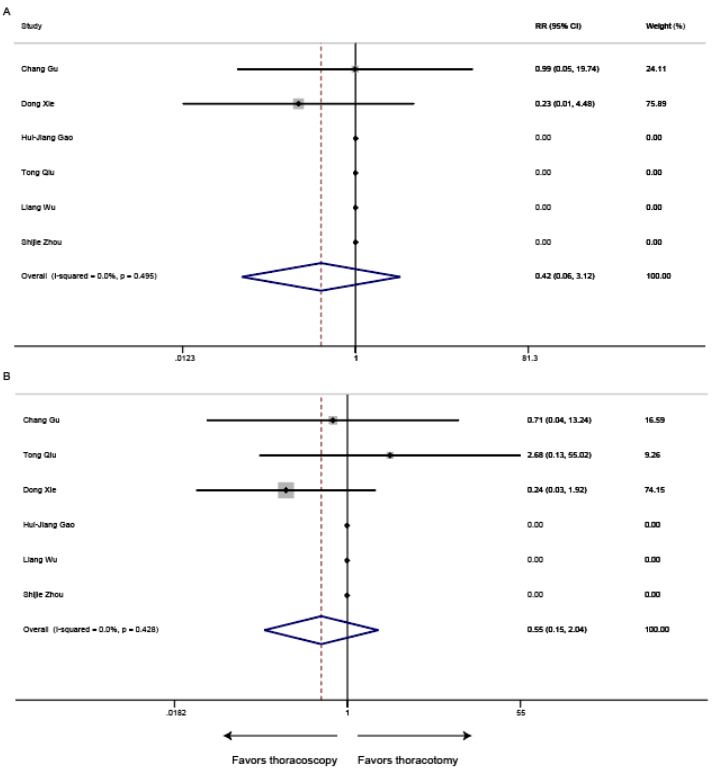
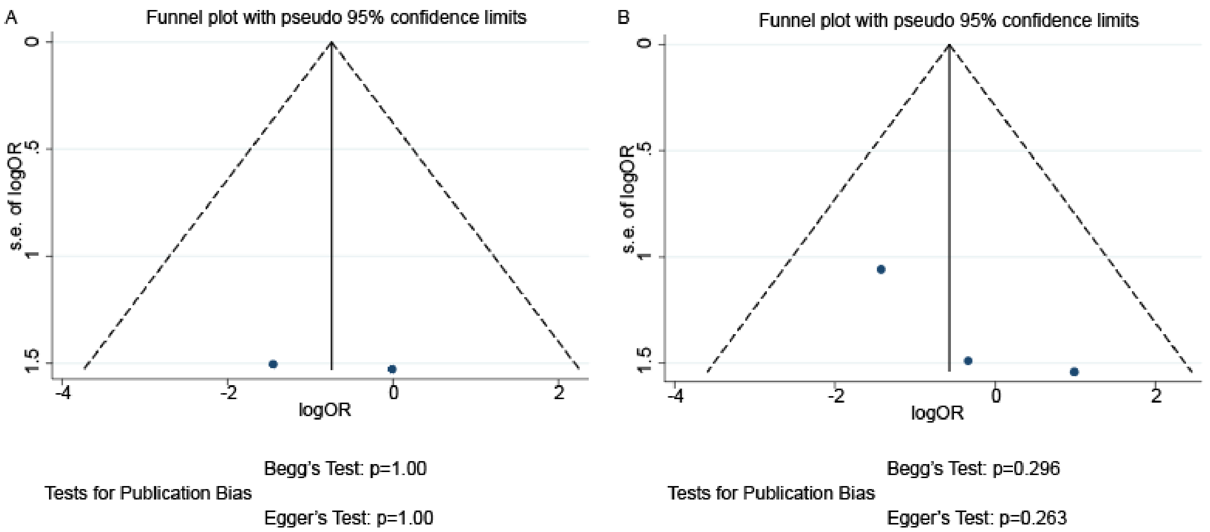


Figure S7. The funnel plot and publication bias tests for 30-day (A) and 90-day (B) mortality of thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included



References

1. Gu C, Pan X, Chen Y, et al. Short-term and mid-term survival in bronchial sleeve resection by robotic system versus thoracotomy for centrally located lung cancer. Eur J Cardiothorac Surg 2018;53:648-55.

Reviewer C

Comment 1: Although not strictly being an issue of the analysis, the results of Robotic sleeve resections in comparison with the open and VATS approaches should be described in greater detail.

Reply 1:

We appreciate this important comment. Sleeve lobectomy is a technically demanding procedure and is only performed in hands of experienced surgeons from large medical centers, which contributes to limited literatures about this surgical approach. Among all 6 included publications in this meta-analysis, only two studies evaluated robotic sleeve lobectomy. Therefore, we may not manage to perform subgroup comparisons among robotic surgery, VATS and thoracotomy in detail.

In this study, robotic surgery and VATS were integrated into the thoracoscopic group when compared to conventional thoracotomy. In addition, in the revised manuscript, we have clarified this issue in the beginning. Even so, the potential bias resulting from the differences between these two surgical approaches are inevitable, which may weaken the robustness of this study, so in this revision, we have additionally discussed this point in the limitation section.

Changes in the text:

Line 130-132: Video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) cases were integrated into the thoracoscopic group for further comparison with the thoracotomy group.

Line 332-336: Additionally, limited by the number of studies investigating thoracoscopic sleeve lobectomy, the uniportal VATS, multiportal VATS and RATS cases were analyzed as a whole when compared with the thoracotomy group and subgroup analyses based on surgical approaches could not be performed, so the potential bias resulting from the differences among these three surgical approaches are inevitable.

Comment 2: If available, data concerning the learning curve of sleeve resections with the two approaches should be reported in greater detail, in particular regarding the number of open procedures performed by the authors before approaching a VATS sleeve lobectomy.

Reply 2:

Thank you for this valuable comment. We think your question on learning curve of thoracoscopic lobectomy is really worth further exploring. The learning curve of thoracoscopic sleeve lobectomy is of great clinical significance, which will provide instructions for thoracic surgeons to learn and master this difficult surgical procedure.

But unfortunately, considering that our study is a meta-analysis based on existing publications and there is no study investigating the learning curve of thoracoscopic sleeve lobectomy, we cannot know how many cases a thoracic surgeon needs to gain experience to learn this difficult surgery. Even so, this question is very interesting and valuable. Actually, we are conducting another original study to investigate the learning curve of thoracoscopic sleeve lobectomy based on data in our center, but the preliminary results have not been drawn. Therefore, we are sorry that we cannot clearly answer this question in here.

Among all 6 included publications, only the study by Xie et al. (1) provided the information about the number of sleeve lobectomy before the conduction of the study. Until the start of their study, a total of 56 VATS sleeve lobectomies were performed. However, considering the nature of the meta-analysis, we are sorry that we cannot provide the number of open procedures performed before approaching a VATS sleeve lobectomy for every involved surgeon.

Comment 3: The type of complications observed with the two approaches should be reported.

Reply 3:

Thank you for this constructive suggestion. We agree with you that it is important to report the type of complication observed with the two surgical approaches. In the revised manuscript, the types of complications among included studies are displayed in Table-S1.

Changes in the text:

Line 202-203: The type and proportion of complications with the thoracoscopic sleeve and thoracotomy sleeve lobectomy were summarized in Table S1.

Table S1 The type and proportion of complications with the thoracoscopic sleeve and thoracotomy sleeve lobectomy

Types of complication	All included cases (n=650)	
	Thoracoscopy (n=281)	Thoracotomy (n=369)
Prolonged air leak	1.83%	2.72%
Cardiac arrhythmia	2.14%	2.71%
Atelectasis	1.21%	1.60%
Pneumonia	4.47%	5.16%
Chylothorax	1.07%	2.34%
Pulmonary embolus	0.71%	0.54%
Bronchopleural fistula	2.06%	1.63%

Subcutaneous emphysema	1.47%	1.31%
Pyothorax	0.71%	0.54%
Bronchial anastomosis bleeding	0.36%	0%
Anastomosis bursting	0%	0.27%
Multiple organ failure	0.36%	0%
Recurrent laryngeal nerve injury	0%	0.27%
Anastomotic stenosis/obstruction	0.44%	0.54%
Postoperative tracheotomy	0%	0.27%
Pneumothorax	1.20%	0.07%
Hemothorax	0.35%	0.27%
Pleural effusion	0.59%	0.93%
Acute myocardial infarction	0.29%	0%
Respiratory failure	0%	0.27%

Note: For propensity matched studies, only cases after matching were included

References

1. Xie D, Deng J, Gonzalez-Rivas D, et al. Comparison of Video-assisted Thoracoscopic Surgery with Thoracotomy in Bronchial Sleeve Lobectomy for Centrally Located Non-Small Cell Lung Cancer. The Journal of Thoracic and Cardiovascular Surgery 2020.

Reviewer D

Comment 1. The title is too long.

Reply 1:

We appreciate this important suggestion. In the revision, the title has been modified to “A systematic review and meta-analysis of thoracoscopic surgery versus thoracotomy for sleeve lobectomy”, which is more concise.

Changes in the text:

Line 1-2: A systematic review and meta-analysis of thoracoscopic versus thoracotomy sleeve lobectomy

Comment 2: Too much miss spellings (especially missed space) and syntax flaws.

Reply 2:

Thank you for this important comment and we apologize for these terrible spelling and syntax mistakes. In the revision, we have carefully checked and corrected the spelling and syntax mistakes and asked a native English-speaking expert to review the wording of this article.

Changes in the text:

Line 67-73:

However, thoracoscopic sleeve lobectomy was associated with longer operation time (SMD = 0.59, 95% CI, [0.14, 1.03], $p = 0.010$). And shorter postoperative hospital stays (SMD = -0.24, 95% CI, [-0.51, 0.03], $p = 0.078$) were observed in the thoracoscopy group with marginal significance. Furthermore, sleeve lobectomy via thoracoscopy could achieve comparable overall survival compared to that via thoracotomy (HR = 0.75, 95% CI, [0.44, 1.06]; $p < 0.001$). In addition, there were no evident publication bias in all observational outcomes.

Line 148-149:

A fixed-effect model was applied if the heterogeneity was acceptable ($p > 0.10$, or $p \leq 0.10$ but $I2 \leq 50\%$);

Line 172-175:

6 studies provided information on operative time of sleeve lobectomy, and heterogeneity was identified in these included researches ($p < 0.001$, $I2 = 83.3\%$). The meta-analysis indicated that patients undergoing thoracoscopic sleeve lobectomy

experienced significantly longer intraoperative operation time (SMD = 0.59, 95% CI, [0.14, 1.03], $p = 0.010$) (Figure 2).

Line 177-181:

Blood loss was evaluated in 6 articles. Compared to thoracotomy, the intraoperative blood loss was similar between thoracoscopic and thoracotomy sleeve lobectomy (SMD = -0.13, 95% CI, [-0.43, 0.18], $p = 0.416$), with evidence of heterogeneity ($p = 0.014$, I2 = 65.1%) (Figure 3).

Line 184-187:

All included researches reported data of number of resected lymph nodes, sleeve lobectomy by thoracoscopic surgery could achieve equivalent performance in intraoperative lymph node resection compared with that by thoracotomy (SMD = 0.02, 95% CI, [-0.19, 0.22], $p = 0.878$), without evidence of heterogeneity ($p = 0.700$, I2 = 0%) (Figure 4).

Line 190-193:

In regard to the postoperative hospital stay, the meta-analysis (6 studies estimated this data) revealed shorter postoperative hospital stays in the thoracoscopic sleeve lobectomy with marginal significance (SMD = -0.24, 95% CI, [-0.51, 0.03], $p = 0.078$). Heterogeneity was observed among included studies ($p = 0.053$, I2 = 54.3%) (Figure 5).

Line 196-199:

5 articles reported data of chest drainage time and our meta-analysis demonstrated that patients receiving sleeve lobectomy via thoracoscopic have similar chest drainage time to those via thoracotomy (SMD = -0.26, 95% CI, [-0.69, 0.17], $p = 0.235$), with specific heterogeneity ($p < 0.001$, I2 = 80.6%) (Figure 6).

Line 202-206:

The type and proportion of complications with the thoracoscopic sleeve and thoracotomy sleeve lobectomy were summarized in Table S1. Of the 6 studies included, the meta-analysis demonstrated that postoperative complication rate estimated by the Forrest plot was similar between two groups (RR = 0.74, 95% CI, [0.51, 1.06], $p = 0.103$), with no evidence of heterogeneity ($p = 0.743$, I2 = 0%) (Figure 7).

Line 209-214:

All 6 included publications provided data of mortality, the meta-analysis revealed that thoracoscopic surgery did not increase the mortality of sleeve lobectomy compared to conventional thoracotomy (30-day mortality: RR = 0.42, 95% CI, [0.06, 3.12], p = 0.394; 90-day mortality: RR = 0.55, 95% CI, [0.15, 2.04], p = 0.367) and no significant heterogeneity was identified among publications (30-day mortality: p = 0.495, I2 = 0%; 90-day mortality: p = 0.428, I2 = 0%) (Figure 8A & B).

Line 217-220:

OS was defined as the duration from surgery to the date of death or last follow-up. 6 studies with 650 patients were included in the analysis of OS. Sleeve lobectomy by thoracoscopy was associated with favorable OS (HR = 0.69, 95% CI, [0.38,1.00]; p < 0.001), without evidence of heterogeneity (P = 0.915, I2 = 0%) (Figure 9).

Line 223-226:

As displayed in Figure 10, no potential publication bias existed in the HRs of OS among studies according to the asymmetrical distribution of funnel plot, which was further identified by the publication bias test (Begg's test, p = 0.806; Egger's test, p = 0.193). Funnel plots of the other results revealed no publication bias (Supplementary material).

Line 236-238:

The feasibility and safety of this procedure have not been fully investigated. Our meta-analysis proved thoracoscopic sleeve lobectomy is a feasible and safe procedure for centrally located NSCLC.

Line 239-248:

Thoracoscopic sleeve lobectomy has experienced evolution toward less operative trauma over the past decades. In 2002, Santambrogio et al. firstly reported thoracoscopic sleeve bronchoplasty. Subsequently, several series of studies reported their experiences in sleeve lobectomy through video-assisted mini-thoracotomy. As experience of the thoracoscopic technique accumulated, sleeve lobectomy was successfully performed by complete VATS in 2008. Thereafter, a series of case reports described complete VATS sleeve resection via three and four ports, the operative duration was reported from 176 to 287 minutes and the postoperative hospital stays were between 3 and 8 days. Over the years, VATS has evolved into a single incision access without rib spreading, which could offer better perioperative outcomes than multi-port surgery

Line 250-251:

With further advancements in operative technique, surgical equipment and anesthesia management

Line 266-267:

six studies investigated the operative safety and oncological adequacy of sleeve lobectomy via thoracoscopic surgery by comparing with that by thoracotomy.

Line 269-270:

Four studies demonstrated that the VATS group experienced significantly longer operative duration than the thoracotomy group

Line 272-273:

While, similar operation time between the thoracoscopic and thoracotomy groups was identified in other two studies

Line 275-276:

But no significant difference between two surgical approaches was observed in the remaining three publications

Line 292-292:

The main reason for the hesitation to perform sleeve lobectomy is the concern about the local recurrence.

Line 311-313:

Additionally, as displayed in Figure 9, our research revealed thoracoscopic sleeve lobectomy can offer a significant advantage on OS over thoracotomy sleeve lobectomy ($p < 0.001$, HR: 0.38-1.00).

Line 351-352:

This conclusion requires confirmation by more large-scale and high-quality researches.

Comment 3: Basically, robot-assisted thoracic surgery (RATS) and VATS are different issues and should be analyzed and discussed individually. This reviewer understood that the studies regarding VATS vs. thoracotomy for sleeve lobectomy are very limited; hence if the authors intended to conjoin the RATS and VATS together, this issue should be clarified at the beginning.

Reply 3:

We appreciate your significant comments. Uniportal VTAS has the advantage of less trauma and rapid recovery compared to multiportal VTAS (1,2). Despite the difference between these two surgical approaches, both multiportal and uniportal VATS have been demonstrated to have significantly better perioperative outcomes and equivalent oncological results compared to conventional thoracotomy in patients with NSCLC (3,4). Therefore, we took these two surgical procedures as a whole in analyses, which is similar to many other studies (5-7). Regarding robotic surgery, two large-sample meta-analysis studies indicated that robotic surgery achieves similar operative outcomes to VATS, and no matter robotic surgery or VATS yields superior outcomes than conventional thoracotomy (5-7). Besides, the studies regarding VATS versus thoracotomy for sleeve lobectomy are very limited. As such, theses three approaches were all taken as the thoracoscopic group when compared to conventional thoracotomy. In addition, in the revised manuscript, we have clarified this issue in the beginning.

Even so, the potential bias resulting from the differences among these three surgical approaches are inevitable, which may weaken the robustness of this study, and in this revision, we have additionally discussed this point in the discussion section.

Changes in the text:

Line 130-132: Video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) cases were integrated into the thoracoscopic group for further comparison with the thoracotomy group.

Line 332-336: Additionally, limited by the number of studies investigating thoracoscopic sleeve lobectomy, the uniportal VATS, multiportal VATS and RATS cases were analyzed as a whole when compared with the thoracotomy group and subgroup analyses based on surgical approaches could not be performed, so the potential bias resulting from the differences among these three surgical approaches are inevitable.

Comment 4: The Discussion is too redundant. Some meta-analysis irrelevant descriptions like the historical aspects (especially like line 267-278) and the evolution of the VATS should be deleted or make them more concise.

Reply 4:

Thank you for this important suggestion. The discussion section in the previous manuscript described too much results from historical publications. Therefore, we have deleted part of descriptions to make them more concise in the revision. However, this study not only aimed to perform the meta-analysis comparing thoracoscopic versus thoracotomy sleeve lobectomy, but also to systematically review the development of thoracoscopic sleeve lobectomy, which could provide readers valuable information about sleeve lobectomy and the development of thoracoscopic sleeve lobectomy. As such, we consider that descriptions for the evolution of the VATS could be retained.

Changes in the text:

Line 278-288:

Discrepancy of operative expertise and impact of learning curve might contribute to the heterogeneity in intraoperative performance. In larger and more experienced centers, sleeve lobectomy via thoracoscopic surgery could confer superiority in perioperative outcomes over that by thoracotomy. Radical lymphadenectomy is of great importance in reducing the late recurrence risk after surgical resection of tumors. For all six included researches, there was no significant difference in performance of intraoperative lymph nodes dissection between thoracoscopy and thoracotomy groups.

In terms of postoperative outcomes, five included studies revealed no statistical difference in postoperative complication rate between the thoracoscopic and thoracotomy groups. Only one research proved lower complication rate after thoracoscopic sleeve resection (30). For all included studies, mortality rate was similar between the thoracoscopic and thoracotomy group.

Comment 5: Although the authors had acknowledged, the 4 limitations mentioned are still the inevitable weakness of this study.

Reply 5:

Thank you for your important comments and we agree with you that the limitations mentioned are still the inevitable weakness of this study. In this meta-analysis, we only included six papers from a single nation, which may weaken the generalization and robustness of our conclusions. However, this limitation may partly arise from some objective conditions. Firstly, thoracoscopic sleeve lobectomy is a technically demanding procedure and is only performed in hands of experienced surgeons from large medical centers, which contributes to limited literatures about this surgical procedure. Besides, due to the large patient population of NSCLC in China, medical centers from China can accumulate more experience than that from other countries, several centers in China have routinely performed thoracoscopic sleeve lobectomy. Therefore, most publications comparing thoracoscopic versus thoracotomy were reported by Chinese centers.

Furthermore, to elevate the reliability of our conclusion, we make comparison on the baseline characteristics of patients including age, sex, BMI, smoking history, FEV1%, tumor location, histological type, pathological T stage and pathological N stage between two surgical approaches in the revision. As shown in Table 2, no significant difference was observed in baseline characteristics between thoracoscopic and thoracotomy sleeve lobectomy. Also, we evaluated the 30-day and 90-day mortality between two approaches and thoracoscopic sleeve lobectomy do not compromise the mortality to thoracotomy sleeve lobectomy.

Admittedly, we cannot determine whether the results of this study can be replicated for different surgeons, institutions or countries. But at least this meta-analysis has achieved significant results in operative time and overall survival, which are new findings different from existing studies. As such, we believe our results have reference value for the following studies investigating the efficacy of thoracoscopic sleeve lobectomy. Finally, we also expect that international large-scale trials in future could confirm our findings.

Changes in the text:

Line 165-169:

Baseline Characteristics

As displayed in Table 2, baseline characteristics of patients including age, sex, body mass index (BMI), smoking history, FEV1%, tumor location, pathological T stage and pathological N stage were all similar between the thoracoscopic and thoracotomy groups.

Table 2 Baseline characteristics between thoracoscopic and thoracotomy sleeve lobectomy

Variables	Number of publications	Test for overall effect		Test for heterogeneity	
		Thoracoscopy vs. Thoracotomy	p value	I^2	p value
Age (SMD [95%CI])	5	-0.01 (-0.19, 0.16)	0.868	0%	0.934
Sex (Male) (RR [95%CI])	6	1.00 (0.88, 1.13)	0.952	0%	1.000
BMI (SMD [95%CI])	5	0.04 (-0.13, 0.21)	0.633	0%	0.971
FEV1% (SMD [95%CI])	4	-0.16 (-0.37, 0.05)	0.145	25.50%	0.259
Smoking (Ever) (RR [95%CI])	6	0.97 (0.83, 1.13)	0.666	0%	0.617
Histological type (SCC) (RR [95%CI])	6	1.00 (0.87, 1.15)	0.981	0%	1.000
Location (Left) (RR [95%CI])	6	1.08 (0.89, 1.30)	0.450	0%	0.928
pT1 Stage (RR [95%CI])	3	1.09 (0.68, 1.76)	0.713	0%	0.497
pT2 Stage (RR [95%CI])	3	1.03 (0.86, 1.23)	0.772	0%	0.811
pT3 Stage (RR [95%CI])	3	1.11 (0.40, 3.08)	0.839	68%	0.044
pT4 Stage (RR [95%CI])	2	0.61 (0.21, 1.76)	0.361	0%	0.489
pN0 Stage (RR [95%CI])	4	1.04 (0.85, 1.27)	0.724	0%	0.976
pN1 Stage (RR [95%CI])	4	0.93 (0.63, 1.37)	0.712	0%	0.518
pN2 Stage (RR [95%CI])	4	0.95 (0.69, 1.32)	0.775	0%	0.775

BMI, body mass index; SCC, squamous cell carcinoma; Note: For propensity matched studies, only cases after matching were included

Figure 8. Meta-analysis: the 30-day (A) and 90-day (B) mortality rate for thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included

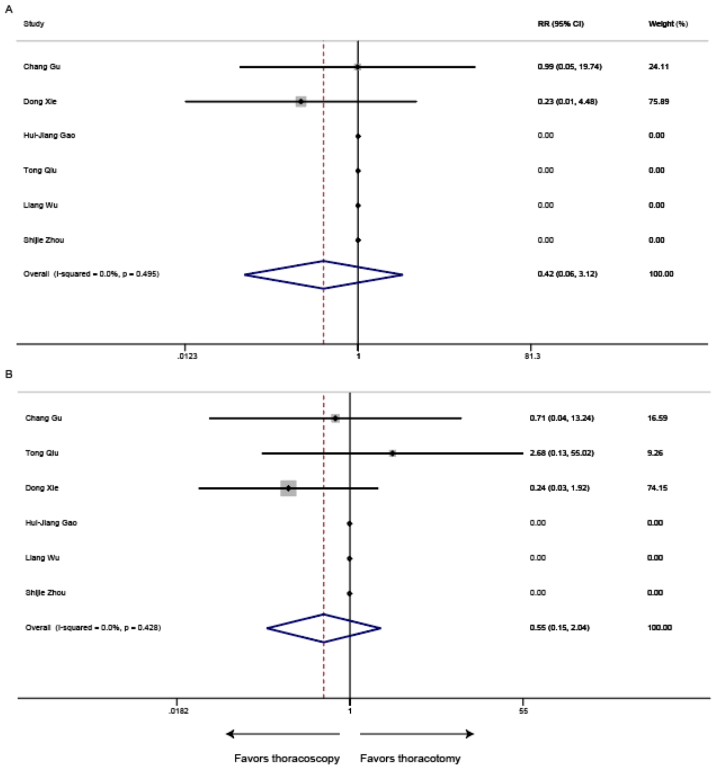
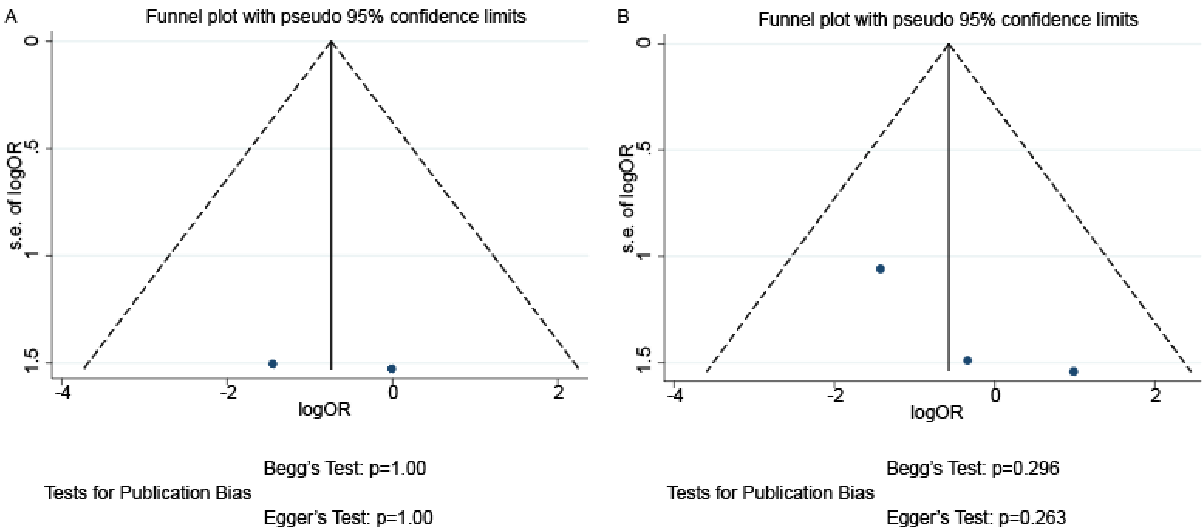


Figure S7. The funnel plot and publication bias tests for 30-day (A) and 90-day (B) mortality of thoracoscopic and thoracotomy sleeve lobectomy; Note: For propensity matched studies, only cases after matching were included



Comment 6: Too much incomplete reference listed.

Reply 6:

Thank you for this constructive suggestion. In the revision, we have removed several incomplete references to make our manuscript more concise.

References

1. Abouarab AA, Rahouma M, Kamel M, et al. Single Versus Multi-Incisional Video-Assisted Thoracic Surgery: A Systematic Review and Meta-analysis. J Laparoendosc Adv Surg Tech A 2018;28:174-85.

2. Harris CG, James RS, Tian DH, et al. Systematic review and meta-analysis of uniportal versus multiportal video-assisted thoracoscopic lobectomy for lung cancer. Ann Cardiothorac Surg 2016;5:76-84.

3. Boffa DJ, Dhamija A, Kosinski AS, et al. Fewer complications result from a video-assisted approach to anatomic resection of clinical stage I lung cancer. J Thorac Cardiovasc Surg 2014;148:637-43.

4. Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg 2009;138:11-8.

5. Ye X, Xie L, Chen G, et al. Robotic thoracic surgery versus video-assisted thoracic surgery for lung cancer: a meta-analysis. Interact Cardiovasc Thorac Surg 2015;21:409-14.

6. Kent M, Wang T, Whyte R, et al. Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database. Ann Thorac Surg 2014;97:236-42; discussion 42-4.

7. Emmert A, Straube C, Buentzel J, et al. Robotic versus thoracoscopic lung resection: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e7633.