

Peer review file

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Reviewer A

Comment 1: The authors said that most of the evidence showed significantly decreased hospitalization costs in the ERAS group. However, as medical health systems are different among countries, the impact of ERAS on medical health systems would not be evaluated. I think the impact of ERAS in the surgical outcomes, i.e. postoperative complications and survival is essential. Additionally, in terms of readmission rates, as the indications of readmission were unclear in these studies, I am afraid that the results of readmission rates would not be reliable.

Reply 1: As the reviewer mentioned, due to differences in medical and health systems between countries, it is really hard to assess the impact of ERAS program on the medical health systems. We have also taken this into consideration, and we have already explained it in discussion part (see Page 20, line 429-434). In fact, our primary purpose for conducting this research is to explore the short-term impact of ERAS program in lung resection surgery, especially the complications after surgery. Additionally, the reviewer was afraid that the results of readmission rates would not be reliable because the indications of readmission were unclear in some studies. We admitted that some of the eligible studies were indeed unclear in terms of readmission rates, which may definitely reduce the credibility of the results. This is also a limitation of our research, and we would like to further explain it in the discussion part (see Page 18-19, line 394-396). We have modified our text as the reviewer suggested in discussion part (see Page 19, line 391-393).

Changes in the text: We have added a sentence to the text in discussion part writing “However, some of the eligible studies were not sufficiently transparent in terms of readmission, which might have reduced the credibility of the results to some extent.” (see Page 18-19, line 391-393).

Comment 2: The ERAS program does not have a standard protocol. Therefore, among studies, the ERAS program is very heterogeneous, especially in systematic reviews and meta-analyses. A potential bias can not be excluded from studies of ERAS.

Reply 2: It is really true as the reviewer suggested that a potential bias could not be excluded due to different ERAS programs applied in eligible studies. The ERAS program is a combination of various procedures from patients' admission through to discharge, aiming at minimizing surgical stress, reducing the occurrence of postoperative complications, decreasing length of stay (LOS), increasing quality of life during hospitalization and thus reduce costs related to surgery. We have summarized the ERAS program elements of each eligible studies in Table 4. The results indicated that the ERAS programs adopted in each study are very heterogeneous, which may cause some inevitable bias and reduce the credibility of our results. This is an important limitation of our research, and we have already explained it in discussion part. To make

this point clearer and easier to understand, we have modified our text in discussion part (see Page 20, line 429-434).

Change in the text: We have modified the text in discussion part writing “Second, the ERAS protocols of the included studies were significantly different, and the implementation standards of the ERAS program varied between each country and region, possibly producing bias and reducing the credibility of the results. In addition, there were differences in patient compliance with the ERAS program (65, 66), which might have led to obvious heterogeneity in the results.” (see Page 20, line 429-434)

Reviewer B

Comment 1: In this manuscript, the authors examined an ERAS program for lung cancer resection could effectively reduce postoperative complications rates and around outcomes. So far as I can tell the authors, this study is a review dealing with a large subject. This is an important result for understanding an ERAS that needs to be widely circulated.

Reply 1: Thank you very much for the reviewer’s comments of our article. Just as the reviewer mentioned that the ERAS program is a combination of various procedures from patients’ admission through to discharge, aiming at minimizing surgical stress, reducing the occurrence of postoperative complications, decreasing length of stay (LOS), increasing quality of life during hospitalization and thus reduce costs related to surgery. Therefore, the implementation of ERAS program for lung surgery should be widely circulated. But our study does have some limitations, especially the included RCTs is too few, which weakened the level of evidence of our subject. We are planning to conduct more RCTs in the future to provide a higher level of evidence to explore the more convincing effect of ERAS in lung resection surgery.

Change in the text: No changes.

Reviewer C

Comment 1: The level of English grammar is moderate and needs more attention. So is the structure of both the introduction and the discussion.

Reply 1: It is really true as the reviewer suggested that the level of English grammar is moderate and needs more attention, because English is not our mother tongue. Therefore, we used AME Editing Service, (<http://editing.amegroups.cn/#editing>) to polish our manuscript.

Change in the text: No changes in content. The changes made by AME Editing Service was marked by using the “Track Changes” function of word processing program. And the changes made by authors was marked by using red color of text.

Comment 2: The rationale for conducting this systematic review is not clear from the

introduction. The authors argue that the inclusion criteria of the systematic review by Li et al. (2017) lead to bias, but do not explain this further. Li's review Li included 7 RCT's, whereas the authors only included 2 RCT's. Because the evidence level based on RCT's is strong, while the evidence level based on cohort studies - which were included in this review- is less strong, the authors should be cautious when drawing conclusions about the effectiveness of ERAS programs.

Reply 2: As the reviewer suggested that the reason for conducting this systematic review is really hard to tell from the introduction part. As a matter of fact, our primary purpose for conducting this research is to explore the short-term impact of ERAS program in lung resection surgery, especially the complications after surgery. Therefore, we have modified our text as the reviewer advised (see Page 6, line 111-114) to make it clearer. As for systematic review of Li et al. in 2017, we found their inclusion criteria did not emphasize the difference between the ERAS group and the control group, just as we written in the text. To be more specific, they included lots of studies that only explored the postoperative impact of a single factor after lung resection surgery (such as preoperative short-term pulmonary rehabilitation training), this may weaken the effect of ERAS program. We believed that this type of studies is not in line with the concept of ERAS and is not suitable for inclusion in our research. Hence, we changed the inclusion criteria that the eligible studies must have a traditional care control group adopting at least three elements fewer than ERAS group to make the conclusion more reliable. It is really true as the reviewer suggested that RCTs do have a higher level of evidence, but there are only 2 RCTs that meet our inclusion criteria. The inclusion of only 2 RCTs did reduce the credibility of our conclusions, so we modified our text as the reviewer suggested in the limitation of discussion part (see Page 20, line 425-429). We are planning to conduct more RCTs in the future to provide a higher level of evidence to explore the more convincing effect of ERAS in lung resection surgery.

Change in the text: We have modified our text into the sentences writing "In order to reach a more substantiated conclusion, we aimed to conduct a systematic review and meta-analysis to determine the short-term impact of the ERAS program on lung resection surgery, especially in relation to postoperative complications." (see Page 6, line 111-114) and "First, the majority of the included studies were cohort studies, and only 2 RCTs were included. Moreover, the majority of eligible cohort studies were separate-sample pre-post-test designs. These types of studies have some limitations, such as nonparallel controls and cohort selection, which might have introduced biases and reduced the reliability of the results." (see Page 20, line 425-429).

Comment 3: The inclusion of cohort studies in this systematic review complements previous reviews on the topic, but the design of these studies needs to be clarified, as do their shortcomings (this limitation is acknowledged in the Discussion but could be better explained). I assume these are separate-sample pre-post-test designs (i.e. studies with measurements before and after implementation of ERAS elements)?

Reply 3: We are very sorry for our negligence of clarifying the design of included cohort studies as well as their shortcomings. As the reviewer mentioned that the majority of included cohort studies are separate-sample pre-post-test designs, this type

of studies does have some limitations (e.g. non-parallel control and problems of cohort selection). Therefore, we modified our text as the reviewer suggested in the limitation part in order to further clarify the shortcomings of this type of research (see Page 20, line 425-429).

Change in the text: We have modified our text into the sentence writing “First, the majority of the included studies were cohort studies, and only 2 RCTs were included. Moreover, the majority of eligible cohort studies were separate-sample pre–post-test designs. These types of studies have some limitations, such as nonparallel controls and cohort selection, which might have introduced biases and reduced the reliability of the results.” (see Page 20, line 425-429)

Comment 4: The aim of the review is not specific. Which outcomes are the authors interested in? The authors describe that this meta-analysis aimed to investigate the effects of ERAS program on surgery of lung cancer. I assume they mean they are interested in the effect on various outcomes after surgery (e.g. complications) rather than the effect on the surgery itself. (In Abstract Part)

Reply 4: It is really true as the reviewer suggested that the aim of this review is not specific. And we are sorry for not clearly clarifying the purpose of the article. As a matter of fact, our primary purpose for conducting this research is to explore the short-term impact of ERAS program in lung resection surgery (e.g. complications, length of stay, mortality and readmission), especially the post-operative complications. In order to make the aim of the review more specific, we have modified the text in abstract part according to the reviewer’s comments (see Page 2, line 33-35).

Change in the text: We have modified our text into the sentence writing “This systematic review and meta-analysis aimed to investigate the short-term impact of the ERAS program on lung resection surgery, especially in relation to postoperative complications.” (see Page 2, line 33-35).

Comment 5: Relevance of primary outcome (postoperative complications) could be described more clearly. (In Introduction Part)

Reply 5: It is really true as the reviewer suggested that the relevance of primary outcome (post-operative complications) was not clear enough in introduction part. The occurrence of postoperative complications is indeed related to many perioperative factors, and there is also relevance between some postoperative complications. In order to make this point clearer, we have modified the text in introduction part according to the reviewer’s comments (see Page 4, line 73-77).

Change in the text: We have added a sentence into our text in introduction writing “The occurrence of postoperative complications is related to many perioperative factors, such as poor preoperative lung function, improper operation by the surgeon, inadequate expectoration after surgery, sputum accumulation, and long duration of chest tube placement.” (see Page 4, line 73-77)

Comment 6: The purpose of the ERAS program is well described, I would propose to add examples of some procedures of the ERAS programs as well. (In Introduction Part)

Reply 6: We are very sorry for our negligence of adding some examples of some procedures of the ERAS program in introduction part. The ERAS program is a combination of various procedures from patients' admission through to discharge, aiming at minimizing surgical stress, reducing the occurrence of postoperative complications, decreasing length of stay (LOS), increasing quality of life during hospitalization and thus reduce costs related to surgery. In fact, we have summarized the protocol of ERAS program for lung resection surgery in Figure 1. But adding some examples of some procedures does make this review more comprehensive. Hence, we modified the text in introduction part according to the reviewer's suggestion (see Page 4-5, line 80-85).

Change in the text: We have modified our text in introduction part into the sentence writing "The Enhanced Recovery After Surgery (ERAS) program, which has become prevalent in recent years, is a multimodal approach encompassing all phases of care: preoperative (including assessment, counselling, nutrition, and smoking cessation), intraoperative (including minimally invasive surgery, standardized anesthetic protocol, and single chest tube placement), and postoperative (including early ambulation, nutrition, and adequate pain relief) (10,11)" (see Page 4-5, line 80-85).

Comment 7: The authors described that the ERAS programs have been widely applied in surgeries of various disciplines: If available, I would propose to add results in these disciplines in terms of the prevention of complications. (In Introduction Part)

Reply 7: This comment of the reviewer is very constructive. At present, the ERAS program has been widely applied in surgeries of various disciplines and achieved good effects. The rate of post-operative complications and LOS were significantly decreased in patients treated with ERAS program in liver surgery, gastrointestinal surgery and spine surgery (Reference 13,14,17). In order to make this review more comprehensive, we have modified the text in introduction part according to the reviewer's suggestion (see Page 5, line 93-96).

Change in the text: We have added a sentence into our text in introduction writing "Moreover, recent studies have indicated that patients treated with the ERAS program during hepatectomy, laparoscopic colorectal surgery, and spinal surgery have a significant reduction in LOS and risk of postoperative complications (13,14,17)" (see Page 5, line 93-96)

Comment 8: The last paragraph could be described more concisely, ending with a clear aim of the study. (In Introduction Part)

Reply 8: It is really true as the reviewer suggested that the last paragraph in introduction part was not concise. In the last paragraph of the introduction part, we intended to describe the findings and limitations of previous systematic review exploring the effects of ERAS program on lung resection surgery, but it seems that our description was too cumbersome. We have re-written this paragraph according the reviewer's suggestion to make it more concise, and the advantages and limitations of previous studies will be described in further detail in the discussion part (see Page 5-6, line 98-116).

Change in the text: We have re-written the third paragraph of introduction as follow

“A recent systematic review and meta-analysis of 38 randomized controlled trials (RCTs) found that the ERAS program plays an important role in reducing the rate of complications and shortening the LOS across various surgical specialties (19). However, the findings of this study may not be applicable to pulmonary resection owing to the limited data. Fiore et al. performed a systematic review and meta-analysis in order to evaluate the efficacy of the ERAS program in elective lung resection in 2016 (20), which included 6 studies (1 RCT, 1 case–control, 4 cohort); however, the authors finally failed to reach a convincing conclusion because of the small sample size and high bias risks. A later evidenced-based review and meta-analysis reported by Li et al. in 2017 (21) that included 7 RCTs, demonstrated that the ERAS program in lung cancer surgery could effectively accelerate postoperative recovery and save hospitalization costs without compromising patient safety; however, the inappropriate inclusion criteria and relatively small sample size might have produced considerable biases and reduced the reliability of their results. In order to reach a more substantiated conclusion, we aimed to conduct a systematic review and meta-analysis to determine the short-term impact of the ERAS program on lung resection surgery, especially in relation to postoperative complications. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist.” (see Page 5-6, line 98-116).

Comment 9: The control group had to adopt at least three elements fewer than the ERAS group. Why did the research team choose for a difference of three elements? For example, in the systematic review by Li a choice was made to include RCTs with a difference of a least 4 ERAS elements between control and experimental group. (In Methods Part)

Reply 9: Our inclusion criteria in this review did include that the control group had to adopt at least three elements fewer than the ERAS group, as the reviewer suggested. We choose this criterion according to a recent systematic review including 38 RCTs across various surgical specialties (Reference 19), and the majority of systematic review on ERAS make it in this way. It should be pointed out that the reviewer may misunderstood the inclusion criteria of the systematic review conducted by Li et al in 2017. The inclusion criteria of their research are that the ERAS program must involve more than 4 elements and encompassing at least 2 phases of perioperative care. They did not emphasize the difference between the ERAS group and the control group (once the ERAS group meet the criteria, the study will be included). Therefore, they included lots of studies that only explored the postoperative impact of a single factor (such as preoperative short-term pulmonary rehabilitation training), this may weaken the effect of ERAS program. We believed that this type of studies is not in line with the concept of ERAS and is not suitable for inclusion in our research. So, we changed the inclusion criteria that the eligible studies must have a traditional care control group adopting at least three elements fewer than ERAS group to make the conclusion more reliable.

Change in the text: No change.

Comment 10: The authors mention that studies with a score higher than 6 on the quality

assessment were eligible for the meta-analysis. Is the outcome of the quality assessment included in the data analysis in any other way? (In Methods Part)

Reply 10: The quality assessment of systematic review and meta-analysis is merely to determine whether this study could be included in our research. The outcome of the quality assessment would not be included in the further data analysis. If a study is of low quality, it cannot be included in the meta-analysis, because it may cause significant bias. In our research, we identified studies with a score equal to or higher than 6 were eligible for our meta-analysis. Under this criterion, we excluded a study with a score of 4. Therefore, all studies eligible for our research were of acceptable quality and make the conclusion more convincing.

Change in the text: No change.

Comment 11: The authors mention that if the SD's were not provided, the studies were not incorporated in the quantitative syntheses. Do the authors mean that the study was not included if only a Median was described? Because the SD can be calculated if the 95CI% is presented. (In Methods Part)

Reply 11: We did not incorporate the data in the quantitative synthesis if the SDs were not provided (even only a Median was described). As the reviewer suggested, we could indeed calculate the SDs through the 95CI%, but the extrapolation of SDs was only applicable for studies with a large sample size and normal distribution of outcomes according to the guidelines of Cochrane Collaborations (Reference 27), just as we have mentioned in the article (see Page 9, line 178-181). We found that the sample size of eligible studies was relatively small and we didn't know whether the outcome data is normally distributed, so we didn't infer the SDs through the 95CI%.

Change in the text: No change.

Comment 12: The authors could consider to describe which ERAS elements were most commonly applied in the studies. (In Result Part)

Reply 12: This suggestion of the reviewer means a lot to us. Describing which ERAS elements are most commonly used in the included studies would indeed make our article more comprehensive. Considering the reviewer's suggestion, we have modified the text in result part (see Page 11, line 231-235).

Change in the text: We have modified our text in results part writing "The most commonly used ERAS element in our included studies was preadmission education/counselling (adopted by 19 studies), followed by early ambulation (adopted by 18 studies). The ERAS elements that were least used in eligible studies were alcohol dependency management and anemia management (adopted by 1 study)." (see Page 11, line 231-235)

Comment 13: It may be interesting to identify which ERAS elements are most effective, or whether the risk of complications decreases if more elements are used. Did the authors consider including this in their analysis? (In Result Part)

Reply 13: As the reviewer mentioned, it is meaningful to further explore which ERAS element is the most effective. However, if we want to conduct a research in this area,

we need studies that only consider one variable between the two groups. Obviously, the studies we included in our research does not meet these conditions. Therefore, it is really hard for us to adopt this suggestion of this reviewer. But this suggestion does point out the direction for our future research, and we intend to explore this issue in depth in our future researches. In addition, the reviewer mentioned whether the use of more elements of ERAS program can reduce the risk of complications. We believe that the effects of ERAS program do not have a clear relationship with the number of elements it uses. There are some elements that play a decisive role in ERAS program (e.g. minimally invasive surgery and postoperative airway management). If one of these important elements are used, the result may be more significant than the use of several minor elements. Hence, we don't think it is very meaningful to implement this analysis.

Change in the text: No change.

Comment 14: The outcome measure for complications used in this study was the Risk Ratio, therefore I think the authors could better describe that the patients in the ERAS group have a lower risk of developing postoperative complications. (In Discussion Part)

Reply 14: It is really true as the reviewer suggested that it could be better to describe that the patients in the ERAS group have a lower risk of developing postoperative complications in discussion part. Therefore, we have modified the text in discussion part according to the reviewer's suggestion (see Page 16, line 336-338).

Change in the text: We have modified our text in discussion part into the sentence writing "we found that patients treated with the ERAS program had a lower risk of developing postoperative complications and a decreased postoperative LOS." (see Page 16, line 336-338). At the same time, we have also modified the corresponding part of the abstract and conclusion.

Comment 15: I would recommend replacing the second paragraph to the paragraph with the limitations (one paragraph with strengths and limitations). (In Discussion Part)

Reply 15: As the reviewer suggested, integrating the advantages and limitations of our research into one paragraph does make the article more organized. However, due to the long length of the strengths and limitations part of our article, combining the two parts into one paragraph may seem very cumbersome and the readers may not have enough patience to read it. Additionally, the majority of high-quality systematic reviews and meta-analyses usually address the limitations of the study at the end of the discussion. After careful discussion among the authors, we really regretted that we have not decided to adopt this constructive suggestion of the reviewer. However, we are very grateful to the reviewer for this meaningful suggestion.

Change in the text: No change.

Comment 16: The start of the third paragraph is a repetition of the introduction. I would recommend to add some information of this paragraph to the introduction (e.g. the different elements of ERAS). In the discussion, the focus should mainly be on the results of this review compared to other studies, and well as the clinical relevance of your results. (In Discussion Part)

Reply 16: In the third paragraph of the discussion, we intended to address the role of stress and inflammation response in post-pneumonectomy complications. Moreover, we demonstrate that ERAS could reduce the incidence of postoperative complications by alleviating these two reactions. However, our description seems to be not concise enough and there is some repetition with the introduction, just as the reviewer mentioned. Therefore, we have re-written this paragraph and move some information to the introduction part according to the reviewer's suggestion (see Page 17, line 359-369).

Change in the text: We have re-written the third paragraph of discussion as follow "Lung surgery can precipitate a series of physical and psychological stress responses, which can cause critical trauma to the body and postoperative complications (54, 55). The ERAS program can effectively reduce the psychological and physical stress of patients, thereby reducing the occurrence of postoperative complications (56,57). Postoperative inflammatory response is the main cause of postoperative complications (58, 59). The study by Dong et al. (32) showed that postoperative inflammatory factors such as interleukin-6 (IL-6) in the ERAS group were significantly reduced, indicating that the ERAS program can weaken the postoperative inflammatory response of patients. Notably, we found that ERAS can effectively reduce the incidence of postoperative cardiovascular complications, which is in contrast to the results of previous studies (20, 21)." (see Page 17, line 359-369). And we have modified our text in introduction part into the sentence writing "The Enhanced Recovery After Surgery (ERAS) program, which has become prevalent in recent years, is a multimodal approach encompassing all phases of care: preoperative (including assessment, counselling, nutrition, and smoking cessation), intraoperative (including minimally invasive surgery, standardized anesthetic protocol, and single chest tube placement), and postoperative (including early ambulation, nutrition, and adequate pain relief) (10,11)." (see Page 4-5, line 80-85)

Reviewer D

Comment 1: I think that postoperative complication was strongly associated with postoperative complications. Therefore, the author should provide the postoperative complications with considering the postoperative complications.

Reply 1: It is really true as the reviewer suggested that there was a strong association between the postoperative complications. However, the links between different postoperative complications are intricate. It is very difficult to perform this analysis based on the data from the studies we have included and our current knowledge of statistics. But we could not deny that this is a very interesting topic for future research. This suggestion does point out the direction for our future research, and we intend to explore this issue in depth in our future researches.

Change in the text: No change

Comment 2: They provided the relationship between the number of ERAS elements and their goals (No 1 to 5 in Results).

Reply 2: As the reviewer suggested that we provided the relationship between the number of ERAS elements and our outcomes in Table 2 and Table 3. But we did not further analysis whether the use of more elements of ERAS program can reduce the risk of complications. Because we believe that the effects of ERAS program do not have a clear relationship with the number of elements it uses. There are some elements that play a decisive role in ERAS program (e.g. minimally invasive surgery and postoperative airway management). If one of these important elements are used, the result may be more significant than the use of several minor elements. Therefore, we don't think it is very meaningful to implement this analysis.

Change in the text: No change.

Comment 3: They commented that they could not analyzed the efficacy of thoracoscopic surgery in this discussion. However, I think that the rete of sublobar resection depend on their goals (No 1 to 5 in Results). They could provide the procedure's data in Results.

Reply 3: This suggestion of the reviewer means a lot to us. As is known to all, systematic review and meta-analysis is a research method that uses the data published by others to analyze and summarize the results. Unfortunately, the studies we included in our research did not separately provide the outcome data for sublobar resection, so it is really difficult for us to conduct this analysis. Undoubtedly, this suggestion is indeed very meaningful and worthy of our in-depth study, and we intend to conduct a RCT in the future to explore this issue.

Change in the text: No change.

Comment 4: The author should provide the ambulation status after pulmonary surgery in each program as Table.

Reply 4: We are very sorry for not clearly explaining the concept of early ambulation after pulmonary surgery. According the latest ERAS guidelines (Reference 24,25), early ambulation means out of bed to chair or walk slowly within 24 hours after surgery. Some of the eligible studies have reported this in the ERAS program, while others did not. We believed that early ambulation should be defined in this way. To make this concept more specific, we have modified the Table 4 according to the reviewer's suggestion (see Table 4).

Change in the text: We have changed "early ambulation" into "early ambulation (out of bed)" in Table 4. (see Table 4).
s and suggestions.