Peer Review File

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Reviewer A:

Comment 1: I liked the idea of summarizing nearly everything that has been done to prevent this complication from happening or to shorten its duration, which is actually more probable than preventing it.
Due to the heterogeneity of procedures, one might find it difficult to organize them in a meaningful way, which the authors actually did twice: once by dividing the procedures into intraoperative and postoperative and, second, by dividing them into invasive and conservative.
On the other hand, I am missing one elegant and from my personal experience, as well as the experience of my colleagues, rather efficacy conservative solution in your review - the instillation of fresh frozen plasma. As far as I am aware, there are at least two publications on it: one with the water seal and another utilizing the digital drainage system. Both showed promising results, which I could confirm, as I have already mentioned, from experience both mine and my colleagues.

Answer 1: We thanks the Reviewer for the useful suggestion. Our search found only two papers on intrapleural instillation of fresh frozen plasma (doi: 10.12659/MSM.895134 and doi: 10.1111/ans.15451) but, unfortunately, none of them is a retrospective case-control or RCT; for this reason, those papers do not meet the inclusion criteria of this review. However, we find this technique worthy of mention, so we added its description in the paragraph “Postoperative PAL conservative management”.

Changes in the text: Lines 207-210.

Comment 2: I would like to see the discussion part with some more meaningful sentences/ideas than simply repeating some previous thoughts (like in lines 246 and 156), or expressing non-founded claims (like in line 254 "..potentially related to additional morbidity..", or general sentence with no actual meaning (line 268 "The adoption of appropriate precautions.." - what would they be??).
To summarize - I expect a re-arrangement of the discussion segment of the paper as well as an addition of the already mentioned conservative measure to the review.

Answer 2: We find the Reviewer’s comment appropriate; we modified the highlighted sentences in order to make them clearer and more meaningful. Moreover, the discussion paragraph has been expanded and re-arranged to better argue the study’s main findings.

Changes in the text: Throughout the text and Discussion section.

Reviewer B:

Comment 1: Aprile et al provide a review of intraoperative and postoperative management of postoperative PAL

The review describes operative techniques that have been studied such as pleural tenting. And, the review includes the role of suction vs. no suction, digital drainage systems and chemical pleurodesis in the postoperative management of PAL. Reviews of these topics have been provided in JTD within the last 5 years.

Answer 1: We thanks the Reviewer for the comment. For this systematic review, we focused on intraoperative APF sealing techniques, surgical approaches to prevent postoperative PAL and postoperative conservative management of PAL; so, we inevitably discussed some already known topics. The aim of our work is to describe every known evidence-based technique to help thoracic surgeons in choosing the more adequate strategy between those described in the vast sea of literature on prolonged PAL management. For this reason, we believe it is better not to leave those topics aside.

Changes in the text: None.

Comment 2: The title of the article somewhat misleading. It should indicate this paper is focused only postoperative air leaks as opposed to air leaks from other causes (i.e. secondary spontaneous pneumothorax). The manuscript does not contrast conservative and invasive management or even define “conservative” or “invasive” management strategies. For example, suction is not necessarily more invasive than water seal.

Answer 2: We agree with the Reviewer’s comment and consequently modified the paper’s Title, by specifying that it is focused only on PAL after lung resections. For “invasive” we meant “intraoperative”; since this term may be misleading, we changed it throughout the whole text. By contrast, for “conservative” we meant “postoperative, non-invasive”; this feature has been changed throughout the whole text to make it clearer.

Changes in the text: Line 1 (Title) and throughout the text.

Comment 3: The role of return to the operating room to manage a PAL versus other measures is only briefly discussed. It is true that there is scant literature comparing re-operation to non-operative management however re-operation should be discussed as an invasive option.

Answer 3: The analysis of the literature on postoperative invasive management of PAL goes beyond the aim of this review, which focuses on intraoperative APF sealing techniques, surgical prevention of PAL and postoperative conservative PAL management. Since this is probably not clear from the Title and the Materials and

Methods section, we tried to modify them to better explain our objectives. Anyway, our search with the described selection criteria did not find any retrospective case-control or study or RCT on this topic.

Changes in the text: Line 1 (Title); Materials and Method section..

Comment 4: The manuscript does not comment on the role of discharge with an indwelling drain which has been reported. Although this may not meet the inclusion criteria for the search, this should be mentioned as an option for management of a postoperative PAL and it is worth citing the relevant literature.

Answer 4: We fully agree with the Reviewer; actually, no studies on this topic met our inclusion criteria. However, we added a mention of this strategy in the "Postoperative PAL conservative management" section.

Changes in the text: Lines 259-275.

Comment 5: The authors should explain why they chose to exclude meta-analysis in this systemic analysis as there are at least three comparing suction versus water seal to manage PAL.

Answer 5: The aim of this study is to provide a systematic review of the original articles comparing a treatment group and a control group. Even if metanalyses are high-quality articles, they don't meet this criterion.

Changes in the text: Not required.

Comment 6: The review of the literature for digital drainage systems is incomplete.

Answer 6: We performed a further search on this topic and find another study meeting the inclusion criteria (Gilbert S, McGuire AL, Maghera S, et al. Randomized trial of digital versus analog pleural drainage in patients with or without a pulmonary air leak after lung resection. J Thorac Cardiovasc Surg. 2015 Nov;150(5):1243-9.). We added this study in Table 2 and in the Results section.

Changes in the text: Lines 247-253.

Reviewer C:

Comment 1: This is an extensive review of PAL-related papers, and the authors must be congratulated for conducting such a complex review with carefully described methodology. I have some objections and suggestions on your methods and also some minor comments on the manuscript. I'd like to thank the authors for reading and considering my review.

1. Your review is focused on 3 very different topics: a) intraoperative prevention; b) postoperative treatment in PAL cases; and c) postoperative prevention/treatment using different modalities and techniques for chest tube management. Trying to conclude on such different topics is quite a difficult mission and, in fact, your review offer no useful conclusions to the reader.

Answer 1: We thanks the Reviewer for the kind and fair comments and suggestions. The aim of our review is to help the thoracic surgeons giving them an overview of the more used and evidence-based techniques to prevent or conservatively treat postoperative PAL. Drawing a conclusion on what technique is more useful is, as stated by the Reviewer, nearly impossible and is not the aim of this work. However, we modified the Discussion section in order to make this issue clearer and to better argument what should be the rationale of choosing one method rather than another.

Changes in the text: Discussion section.

Comment 2: Suggestion: why not focusing your excellent review on PREVENTION and excluding from it postoperative techniques for the TREATMENT of Pal cases? Doing so you could divide your analysis in a) intraoperative, and b) postoperative prevention strategies, and not in therapeutic methods in cases having postoperative PAL.

Answer 2: We are very pleased with the Reviewer's opinion on our paper and grateful for the suggestions. Actually, we think that focusing only on prevention would lessen the study value, but we decided to rearrange the manuscript's design in order to better and separately argument both topics.

Changes in the text: Throughout the text.

Comment 3: If you do so, you'd need a rather deeper analysis of papers focused on modelling the risk of PAL. IN your text, you are just stating (line 256) that PAL is rather unpredictable, but there are some publications on different predictive models that could enrich your manuscript (some examples at: doi: 10.1016/j.athoracsur.2003.10.082 ; doi: 10.1016/j.ejcts.2004.11.004 and doi: 10.21037/tlcr-21-186).

Answer 3: Postoperative PAL risk factors have been already largely and excellently described and analyzed by other Authors; we tried our best to focus on intraoperative prevention measures and postoperative PAL conservative management. Nevertheless, we agree with the Reviewer on the necessity of incorporating the knowledge on predictive factors of PAL in our manuscript to make the subsequent arguments clearer to follow and understand. Moreover, we re-analyzed the included studies to search for any differences in results between "high-risks" and "non-high-risk" groups and added the available data in the Tables.

Changes in the text: Lines 72-73; 290-295; 318-321, Tables 1 and 2.

Comment 4: Your PICO question is arguable, since the "Intervention" includes: "various measures adopted to manage the air leak both intra and post-operatively" but not all modalities/technologies of chest tube management are focused on cases having air leaks; besides, intraoperative measures are focused on prevention, not management.

Answer 4: We agree with the Reviewer and properly modified the "Intervention" in the PICO questions by specifying that we took into account also intraoperative prevention strategies and not only intraoperative management of PAL.
For what concerns the chest tube management, we couldn't find in literature any study describing this issue only in patients with PAL. So, we selected only those studies reporting data on PAL and/or chest drain duration after the use of digital drainage or suction application, compared to standard drainage system (water seal). Tables and text have been corrected by focusing on the results obtained in the patients with PAL and deleting data on PAL incidence, that can be misleading.

Changes in the text: Lines 127-135, Table 2.

Comment 5: In Table 2 you are presenting intraoperative and postoperative methods for treating PAL cases along with strategies of pleural drainages in cases without PAL (suction or not, alternate suction, digital systems, etc). The title of your Table 2 is: "Comparative table of post-operative measures to manage prolonged air leak" but you are including a sub-heading entitled: "Chest drain management" and all papers including in the review are not focused on PAL cases but are comparing the prevalence of PAL in two cohorts having different kinds of chest drain management. The same problem with a couple of papers comparing the use of digital systems in lung resection cases.

Answer 5: As previously written, we edited Table 2.

Changes in the text: Table 2.

Comment 6: Minor comments:
6a) If you consider my previous comments your title should better be: "Intraoperative and postoperative prevention of PAL, etc"

Answer 6a: The Title has been modified as suggested by the Reviewers.

Changes in the text: Line 1.

6b) Ask a professional to proofreading and editing your manuscript.

Answer 6b: The manuscript has been extensively revised by an English native speaker.

Changes in the text: Throughout all the text.

6c) Line 135. "Outcomes: reduced PAL duration or decreased APF incidence, shortened chest drain stay and hospitalization". I believe you meant: shortened chest drain durantion and ostoperative heospital stay.
Line 137: Instead of" both retrospective studies with a control group", the correct epidemiological term would be "retrospective case-control studies".
Line 153: Should this heading be: Intraoperative instead of Invasive?
Line 212: You wrote: "Brunelli and colleagues wrote many papers…" but just 3 are referenced. Why not rewording as "Brunelli and colleagues wrote three papers…"

Answer 6c: The text has been corrected according to the proper Reviewer's suggestions.

Changes in the text: Throughout the text.

Reviewer D:

This manuscript is a systematic review of clinical data of prolonged air leak (PAL) using PRISMA. Thirty-eight papers were selected. Intraoperative measures as surgical sealants, pleural tenting, proper management of the chest tube and the use of blood patch sclerosant agents seems to reduce postoperative air leaks and length of hospitalization.

I have the following concerns.
Comment 1: The risk of postoperative air leak differs significantly between patients with COPD and those without COPD. The present study is a mixture of both of the COPD patients and non-COPD patients, making it difficult to draw conclusions; I believe it is better to focus on COPD and other high-risk patients.

Answer: We agree with the Reviewer's comment. Nevertheless, restricting the search to those articles reporting only on COPD patients, or comparing results of COPD vs non-COPD patients, would mean an excessive reduction of this review's bibliography. However, we searched information about COPD patients in the selected studies and included these data in the Tables.

Changes in the text: Table 1 and 2.

Comment 2: Lobectomy, segmentectomy, and wedge resection have different risks of postoperative lung leakage. The data are mixed and it is difficult to draw conclusions from this.

Answer: We find this suggestion very useful; the text and the Tables have been edited and the type of surgery has been specified to better evaluate the different PAL risk.

Changes in the text: Table 1 and 2.

Comment 3: Treatment strategy differ between APF and BPF. This study should focus on APF only.

Answer: We apologize if the aim of this review was not clear. Our work focuses only on PAL due to APF and this issue has been specified in the "Materials and Methods" section.

Changes in the text: Lines 88 – 115.

Reviewer E:

Thank you for submitting this well written concise, systematic review on PAL.
I have some comments/questions:

Comment 1) Did the authors look into further data on Talc and bleomycin?
They commented on iodine and doxycycline, but did not mention any studies on talc, which there are several, could that be included in the data?

Answer 1: We thanks the Reviewer for the suggestion. Actually, we searched the literature for studies on post-lung resections PAL treatment with chemical pleurodesis by talc or bleomycin, and can't find anything but studies on malignant pleural effusion management. For this reason, we unfortunately couldn't mention those methods in our systematic review.

Changes in the text: None.

Comment 2) Also did the authors find, wedge vs. lobe vs. segment and the differences for PAL?

Answer 2: We thanks the Reviewer for this comment; the bibliography has been revised to find details on the type of surgery. The text and the Tables have been properly modified.

Changes in the text: Table 1 and 2.

Comment 3) Can the authors further explain digital drainage vs. the standard slightly as this a newer concept to many, thank you

Answer 3: We added some information on digital monitoring of chest drainage in the "Postoperative PAL conservative management" section.

Changes in the text: Lines 240-242.

Very nice study showing that there are many techniques that can be helpful but a long way to go.

Reviewer F:

While prolonged air leak (PAL) after pulmonary resection is a major factor in keeping patients in bed and in delaying, and early hospital discharge, most of literature about PAL is focused on the potential prognostic factors leading to PAL rather than on its management. This systematic review focuses on the latter. Therefore, this systematic review is logical and interesting, and discussed a hot topic in thoracic surgery. However, the following points should be addressed.

Comment 1: The title is confusing to readers. How about "perioperative management of PAL: a systematic review"?

Answer 1: We agree with the Reviewer, the title has been modified according to all the Reviewers' suggestions.

Changes in the text: Line 1.

Comment 2: Was it enough to search the literature in PubMed and Cochrane Library? (ScienceDirect, EMBASE, Ovid MEDLINE, Scopus, and Google Scholar etc.)

Answer 2: We thanks the Reviewer for the suggestion. Other database and online libraries were searched, as reported in the text, and bibliography has been updated.

Changes in the text: Lines 93-94.

Comment 3: Assessment of risk of bias in included studies should be shown in the methods section.

Answer 3: Risk of bias was assessed using the Cochrane tool, as already stated in the "Materials and Methods" section and in Supplementary Table 1.

Changes in the text: None.

Comment 4: The intraoperative repair is often performed with an application of both fibrin glue and polyglycolic acid (PGA) sheets. Several studies have reported that the PGA approach was associated with lower rates of PAL as compared to the non-PGA approach.
Ueda et al. J Thorac Cardiovasc Surg 2010;139:600-5
Yano et al., World J Surg (2012) 36:463–467

Answer 4: We thanks the Reviewer for the useful suggestion; the abovementioned studies have been evaluated, inserted in the "Results" section and described in Table 1.

Changes in the text: Lines 171-174, Table 1.

Comment 5: While the rate of PAL requiring reoperation after general thoracic surgery procedures is low, could the author discuss how we can select the patients for repair by re-do operation?

Answer 5: The analysis of the literature on postoperative invasive management of PAL goes beyond the aim of this review, which focuses on intraoperative APF sealing techniques, surgical prevention of PAL and postoperative conservative PAL management. Since this is probably not clear from the Title and the Materials and Methods section, we tried to modify them to better explain our objectives.

Changes in the text: None.