Peer Review File

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First External Peer Review

Reviewer A

The manuscript deals with a very interesting topic: What treatment should we advocate for if a patient is eligible for both EBV and LVRS.
It is well structured, well written and very understandable for the reader. It reports a single center surgical experience including a relatively large number of patients (n=88) considering a study period of 5 years and a statistical pairwise matching. The analysis is carried out in a very understandable and statistically correct manner.
I have no major concerns.

Comment 1: The text mentions in the methods (line 176) that all procedures were only carried out unilaterally. Does this mean that the patient never had a subsequent treatment of the second (less affected side)? This would be a rather uncommon approach. Please elaborate. Of the 88 matched patients, where there any which had two different treatments at different timepoints (EBV on one side followed by LVRS ipsi- or contralaterally for example)?
Reply 1: Thank you very much for this valid comment. Regarding the unilateral procedures we meant that in our department we do not offer bilateral procedures simultaneously i.e., on the same go as used to be the case with sternotomies. In the EBV group, 2 patients had to have their valves removed because of bleeding and hence those 2 patients had then LVRS. In the LVRS group 2 patients had LVRS which was on the contralateral side, but this was perceived as a separate treatment with a new entry rather than a re-intervention and the CAT improvement was measured from after the initial side was done. These are better explained in the text.
Changes in the text 1: Changed in the text in the Results section, Page 12, Paragraph 7, Line 254 and better clarified in the Patients and Methods section, Description of interventions subsection, Page 8, Paragraph 3, Lines 179-182.

Comment 2: The reason for exclusion of 42 patients from matching is not sufficiently explained. Was it because of prior chartis measurements or inexistent fissures in the CAT? Please elaborate.
Reply 2: This is a valid point, and we thank the reviewer for it. The 42 patients were excluded because they were not deemed as candidates for both procedures either because of fitness ie., not for LVRS or because of StratX/CT thin slice analysis showed not completed fissures and

therefore the patients could not have EBV. Therefore, the patients could not have both modalities offered as a first intervention and as such were excluded from the study.
Changes in the text 2: Explanation added in the Patient and methods section, Methods subsection, Page 5, Paragraph 1, Lines 114-116.

Comment 3: Lung transplantation as an additional treatment modality of end-stage emphysema is not mentioned in the manuscript. Where some patients in this cohort (n=153) eligible for transplantation or even "bridged to LuTX" by means of EBV or LVRS? Lung volume reduction can potentially impact the perioperative outcome after LuTX as shown in a very recent publication (DOI: 10.3389/ti.2022.10048) and it would be important to the reader to mention if any of the 88 patients was referred to LuTX later on.
Reply 3: This is an excellent point. To our knowledge none of the patients included in the study had transplantation as at the time of data accumulation patients were referred to the local transplantation service before they were added to the list for LVR intervention. Therefore, the outcomes are solely due to LVR intervention without any lung transplantation in the course of events.
Changes in the text 3: Explanation added in the Patient and methods section, Methods subsection, Page 6, Paragraph 2, Lines 122-123.

Reviewer B

In the manuscript entitled "Impact of the type of initial intervention on the outcomes of Lung Volume Reduction for emphysema: a propensity matched study", the authors aimed to compare the outcomes between lung volume reduction surgery (LVRS) and endobronchial valve (EBV) treatment as treatment modalities for patients with severe emphysema. The authors used propensity scores to construct two comparable groups, which I believe is the fairest way the authors could construct the groups retrospectively. However, this study has a number of real shortcomings, the main being the lack of objective data after treatment (e.g. pulmonary function data and exercise capacity). This limits the clinical use of the data presented in this study. Furthermore, a clear red line in the manuscript is missing and some parts are difficult to read especially due to the lack of clear structure in the method and results section, which in turn also translates to the discussion.

Major revisions

Comment 1: The manuscript, especially the methods and results, could use some (re)structuring and could be written more concisely (3632 words is a lot). Additional subheadings might help and to shorten some sentences (for example the sentence that stretches from line 139 to 155). It might also help to write the results in the same order as the endpoints were defined.

Reply 1: Thank you for the valid comment. We have shortened the whole manuscript as per your recommendation and we have re-written the results according to endpoints swapping figure 2 and 3 around to capture this change of results presentation. We have decreased the manuscript hopefully adequately by removing paragraphs and by writing more concisely. The overall word count now is 2978 but we had to add parts as per the other reviewers' suggestions. We hope you find the changes adequate.

Changes in text 1: Whole manuscript changed as per the recommendations. Figures 2 and 3 were swapped around as per reviewer's suggestion.

Comment 2: In the abstract the authors wrote "the median follow-up was up to 84 months", but this is not true. There median follow-up was 32 months and the maximum follow-up duration was 84 months.

Reply 2: Thank you for this comment. It is correct and we apologize for the mistake. The correct numbers have been reported in the manuscript.

Changes in text 2: Changed in the Abstract section, Patients and Methods subsection, Page 3, Paragraph 2, Lines 57-58.

Comment 3: What is meant by exercise tolerance? In method section the authors describe: "as noted during a 6 minute walking test or as documented by the physician in the notes", but the reported distances is I believe not the 6-minute walk distance, otherwise it is significantly lower than the 6MWD found in other studies.

Reply 3: Thank you for the valid comment. Most of the patients had a 6 minute walking test and this is reported in the study. In some occasions though we could not find a 6 minute walking test but the physician/surgeon who reviewed the patient had written in the notes the walking distance ability of the patient. There was a mistake in reporting the actual numbers (example 89 meters instead of 189 meters possibly by mistake while writing the manuscript) and these are now changed in the manuscript. The standard deviations seem to be correct so apologies for this mistake.
Changes in text 3: Exercise tolerance correctly presented in the Tables section, Tables 2 and 3, Pages 24 and 25.

Comment 4: The legend of figure 2, I believe, is not the correct legend but is the one for figure 3 which does not have a legend at all. Furthermore, these figures seem to be made using R statistics. If so this should be mentioned in the method section.
Reply 4: Correct comment and we thank the reviewer for this. Figure 1 was indeed without a legend by mistake and this has now been added in the figure legends. Similarly, the correct legends are matched with the correct figures. The use of R is mentioned in the appropriate section.
Changes in text 4: Figure 1 legend added in Figure Legends section, Page 22, Paragraph 1, Line 476 and figure 2 and 3 legends were matched with the proper figures in the Figure legends section, Page 25. Also, use of R program was mentioned in the Analysis section, Page 10, Paragraph 2, Lines 211-212.

Comment 5: The authors claim that the results of their study will be invaluable for physicians and surgeons who will have to decide between EBV treatment and LVRS. This is a very bold statement based on very limited objective data. There is no data on the difference in improvement in pulmonary function, exercise capacity or quality of life, which will have a major impact on the choice. Furthermore, the authors themselves also describe that based on their results they cannot make a clear guideline. Thus, the results should be interpreted with more caution.
Reply 5: Thank you for your comment. It is a valid comment and we totally agree that the results from this study are only indicative. As such this sentence was removed from the manuscript.
Change in the text 5: The sentence was removed from the Discussion section.

Comment 6: What is the reasoning behind the cox proportional hazards analysis on predictors for re-intervention?
Reply 6: Thank you for this correct comment. We perceived re-interventions as an important endpoint in this study and because EBVs showed more re-interventions we tried to identify factors correlating with this finding. However, the reviewer is correct to imply that this analysis does not make much sense since the primary endpoint is survival and as such we decided to

remove the cox analysis from this present manuscript but kept the analysis of re-interventions by time as this we felt would help show that one event does not induce a second event. We hope that you will agree with this decision.
Changes in the text 6: All analysis regarding the predictors was removed from the manuscript.

Comment 7: In the discussion the authors state that re-intervention was an important outcome for multiple reasons. They mention a financial aspect and a direct correlation with quality of life. The NICE guideline on COPD (Dec, 2018) summarizes that LVRS costs around 98,400 GBP/QALY and EBV around 21,900 GBP/QALY, thus it is questionable if overall LVRS is financially beneficial taken the significant higher number of re-interventions after EBV treatment. Furthermore, they did not include a reference on this direct correlation between re-intervention and quality of life and these results are not shown in this study, but this claim should be substantiated.
Reply 7: Thank you for this valid comment. The line has been removed from the manuscript in agreement with your valuable comment.
Changes in the text 7: Lines removed from the manuscript in the Discussion section and changes made in the Discussion section, Page 14, Paragraph 5, Lines 305-307.

Comment 8: The authors also state that there is a correlation between efficiency and overall success of the modality (line 304-307), based on what do they claim this correlation?
Reply 8: We would like to thank the reviewer for this question. We agree that it was not reiterated correctly and as such it is now erased from the manuscript.
Changes in the text 8: Lines removed from the manuscript in the Discussion section.

Comment 9: The authors state that the pneumothorax rate after EBV that was found in this study (16%) was lower than the rate of around 30% reported in the literature. However, the pneumothorax rate reported after EBV treatment is around 4-27%, so 30% is really the upper limit. As reference the authors use one LVRS study (ref 17), thus this is not a correct reference to for the pneumothorax rate after EBV treatment.
Reply 9: Thank you for identifying this valid discrepancy. Indeed by mistake the wrong citation was mentioned next to this comment and we apologize for this. We have also restructured this sentence as per the reviewer's guidance.
Changes in the text 9: Changed in the Discussion section, Page 14, Paragraph 4, Lines 303-304.

Minor revisions
Comment 10: In the introduction the authors write "Lung volume reduction for emphysema (LVRS or EBVs) can have a survival benefit over medical treatment in appropriately selected patients" and the reference used for EBV treatment is the VENT trial (ref 4). In this trial there

was no significant difference in 12-month survival between the SoC and EBV group. Furthermore, this main aim of this study was safety and efficacy. There are more dedicated papers that studied survival after EBV treatment.
Reply 10: Thank you for your valid comment. Reference 4 has been changed with a more recent and appropriate study underpinning the above mentioned.
Changes in the text: Reference 4 changed in Reference section, Page 18, Lines 395-397.

Comment 11: The authors state that they used the STROBE guideline in the introduction but this is better mentioned in the methods.
Reply 11: Many thanks for pointing this out to us it is a correct remark however the journal asks for this to be mentioned at the end of the Introduction section. This is the reason why we placed the STROBE guidelines in the Introduction section. We are of course happy to abide with what the reviewer would like us to do provided that this will be acceptable by the journal.
Changes in the text: None at this point.

Comment 12: Reference 7 contains a link to the NICE guidelines. However, this link is to the old guidelines from 2010, there is an updated version (2018).
Reply 12: Thank you for your correct comment. We have changed the reference appropriately.
Changes in the text: Reference 7 changed, References section, Page 18, Lines 404-405.

Comment 13: Were EBV kept in all patients or were they permanently removed in some. If so, in how many patients and why. And did these (some) of these patients subsequently received LVRS?
Reply 13: Many thanks for this comment. The valves were permanently removed in 2 cases as they caused bleeding and both patients had subsequently LVRS.
Changes in the text: This is better clarified in the Results section, Page 12, Paragraph 7, Line 254.

Comment 14: Table 4: what is meant by ‘substance induced lung pathology’?
Reply 14: Thank you for asking this valid question. It is meant lung pathology induced by cannabis as this was often captured in the notes of patients.
Changes in the text 14: Changed in Tables section, Table 4, Page 25.

Comment 15: The p-value is missing in figure 2.
Reply 15: Thank you for this important comment. Our statistician was able to provide a p-value for the Nelson Aalen analysis at .766.
Changes in the text 15: Added in the Results section, Page 11, Paragraph 5, Line 249 and also in figure 3.

Comment 16: I would suggest to add the change in CAT score to table 2 and to test if this is significantly different between the LVRS and EBV groups. What is described in the text is only that the CAT score significantly improves after treatment and that this is not the case for EBV. However, it is not shown that the change in CAT score between those groups is significantly different. Nevertheless it is claimed in the discussion that the improvement in breathing ability is objectively proven by CAT scores. Furthermore, the CAT score is not a measure for breathing ability only, but for the overall health of COPD patients.
Reply 16: This is a correct and valid point. CAT score added in the Table 5 as per your request and this was proven to be different.
Changes in the text 16: Added in Table 5, Tables section, Page 27, and also changed in the text in the Results section, Page 12, Paragraph 11, Lines 271-276.

Comment 17: I would not refer to a table in the discussion (line 286), but describe what your main results are.
Reply 17: Very valid comment and we thank the reviewer for this. We have erased the mentioning of the table from the Discussion section and described the main findings.
Changes in the text 17: Erased from the Discussion section.

Comment 18: In the discussion there is a lot of emphasis on the 'improved breathing ability'. However this is an unvalidated measure thus it is unknown if it gives insight into the quality of life (311).
Reply 18: This is a valid comment. We have altered the Discussion section without any focus on presenting the breathing quality aspect but mentioning overall health/quality of life way.
Changes in the text 18: Changes done throughout the discussion section.

Comment 19: Line 371 – 373: references are missing.
Reply 19: Thank you for your correct comment. The references were added at the end of the sentence.
Changes in the text 19: The references were added in Discussion section.

Comment 20: Line 375-377 about the CELEB trial should be mentioned, but where it is now placed in the discussion does not make a lot of sense to me.
Reply 20: Thank you very much for this valid comment. We have moved the comment regarding the CELEB study to a place in the discussion which would make more sense if you would agree.
Changes in the text 20: CELEB study comment moved in the Discussion section, Page 16, Paragraph 11, Lines 395-397.

Comment 21: Not all used abbreviations are defined at first mention: line 96 LVRS and EBV; line 99 MDT; line 150 LOS. Furthermore, MDT is not defined in table 5.
Reply 21: Thank you for identifying this discrepancy. LVRS and EBV, MDT and LOS were first mentioned in the abstract section and for this reason we did not re define them in the text. We have done this however for Table 5 as MDT was not defined under the table. We hope the reviewer agrees with this but we will be happy to change all these and redefine if needed.
Changes in the text 21: MDT defined in the Tables section, Table 5, Page 27.

Comment 22: In line 153 it seems like a word is missing: all data were collected
Reply 22: Thank you for identifying this missing word which has been added as per your suggestion.
Changes in the text 22: Added in the Patients and methods section, Data subsection, Page 6, Paragraph 1, Line 132.

Comment 23: In line 213 there is a typing error: if = of.
Reply 23: Thank you for identifying this error. We have corrected it in the manuscript.
Changes in the text 23: Changed in the Patients and Methods section, Analysis subsection, Page 10, Paragraph 3, Line 217.

Reviewer C

The insights from Your retrospective analysis are urgently needed to better understand the pro´s and con´s of these two different treatment options, as a relevant number of patinets qualify for both. And You put much effort in proper methodology. This makes Your research very valuable.

I have only some minor remarks:

Comment 1: You put much emphasis on "breathing ability" and You state in the discussion, that the documented changes after therapy are a "very important finding" (line 310). You should, however, describe in more detail in the methods section, how breathing ability was assesed. Was it just interviewing the patient? In this case it might be difficult to get comparable results in a retrospective data collection over a period of several years, were many different doctors might have interviewed patients and might have documented findings in different ways! Or has a standardiezed scale or tool been used (other than CAT)? This seems especially important, as You don´t have PFT´s in the follow up and much of Your efficacy assessment is based on "breathing ability". If there was no standardised tool, this should be discussed as a limitation.
Reply 1: Thank you for this valid comment. Unfortunately, many clinicians were practicing differently i.e. were not performing postoperative lung function tests in an organized manner. Reviewing the notes however, all patients had CAT score calculated at least and had extensive discussions as to how much different their breathing and overall health and quality of life had been changed throughout the study. We think that you have a good point that our investigation is not about breathing improvement per se but overall quality of life improvement which would be additionally better aligned with the calculation of CAT scores. Hence, we have changed the “breathing ability” to overall quality of life” post intervention as this would be better addressed with the measured CAT score as said before. Unfortunately, as is the case in many institutes, in our department there were no uniform post-intervention investigations and as such lung function tests or 6MWTs were not routinely performed after the interventions. We have also added these as limitations.
Changes in the text 1: Changes made throughout the Discussion section ie Page 13, Paragraph 1, Lines 287-288; Pages 13-14, Paragraph 3, Lines 297-300; Page 15, Paragraph 10, Lines 335-338; Page 16, Paragraph 12, Lines 352-354. Changes were also done in the Results section, Page 12, Paragraph 11, Lines 271-276. Finally, changes were done in the Patients and methods section, Study design subsection, Page 9, Paragraph 2, Lines 199-200.

Comment 2: Figure Legends: Figure 1 has no legend. Legend for figure 1 belongs to figure 2, and legend for figure 2 belongs to figure 3.
Reply 2: Thank you for picking up this discrepancy. We have already corrected this based on previous reviewer comments.

Changes in the text 2: None at this stage as this has already been done previously i.e. figure 1 legend was added and the rest of the figure legends were matched with the actual figures. Please note that figures 2 and 3 were swapped around as per another reviewer's request.

Comment 3: You should give more details regarding the kind of surgery: have You performed upper lobe shaving? Have there also been lobectomies? Have You surgically treated only upper lobes?
Reply 3: Thank you for your correct comment. We have not performed any lobectomies and only upper lobe emphysema LVRS have been included in this study. These have been added in the manuscript.
Changes in the text 3: Added in the Patients and methods section, Description of interventions subsection, Page 8, Paragraph 1, Lines 170-171, and in Patients and methods section, Description of interventions subsection, Page 8, Paragraph 3, Lines 179-182.

Comment 4: You also should give information on how the 7 pneumothoraxes in the EBV group were managed. I suppose, that the majority has required the placement of a chest tube? How were drainage times? Placement of a chest tube should probably also be counted as a re-intervention?
Reply 4: Thank you for the correct comment. A chest drain was inserted in 4 cases but in the other 3 the pneumothorax was small and was chosen to be observed without any intervention needed. We have considered insertion of chest drain for development of pneumothorax re-interventions as you have correctly suggested. This has been added variably in the text. The median number of total interventions however remained the same hence no change was done in Table 5.
Changes in the text 4: Clarified in the Patients and methods section, Data subsection, Page 7, Paragraph 3, Lines 154-155 and in the Results section, Page 12, Paragraph 7, Lines 255-256 and Page 12, Paragraph 9, Lines 264-265.

Comment 5: There is also a discrepancy in Your paper regarding the assessment of morbidity: In the results section You state, that "morbidity was similar" in the two groups (line 256). This statement is made with regard to the pure number of events. In the discussion You state, that in the surgical group "morbidity was more severe and led to more complicated surgical re-interventions" (line 321). This is said with regard to severity of the events. This discepancy has to be resolved in some way. Especially, as You conclude, that LVRS is not more "dangerous" than EBV. In principle I agree with this conclusion. But it has also to be plausible from the data. If You have the same number of events, but in one group events are more severe, You can´t conclude, that morbidity ist the same. For example You could grade the events according to their severity. An event being severe, if it prolongs hospital stay, causes permanent damage etc... (criteria usually used for SAE´s in clinical trials). And than reevaluate, whether graded morbidity is still the same between groups. Or You could more emphasise on the management

of pnemothoraces in the EBV group, wich also causes morbidity burden (see above). And could then justify the conclusion "morbidity was the same".

Reply 5: We thank you for this important comment. Overall morbidity was indeed the same but the type of treatment needed was different as we would have expected. The treatment in both groups ended up in re-interventions and in most cases in a new general anaesthetic and reoperation. Therefore this paragraph was re-written to represent this better.

Changes in the text 5: Changed in the Discussion section, Paragraph 4, Page 14, Lines 301-304.

Reviewer D

Really good paper, easy to read.

I note that there's a poor 30 day mortality, despite 44 pts per group, which indicates a great expertise of your center for lung redution volume.
Comment 1: - you failed to demonstrate difference between ebv and lvrs for re intervention, maybe because of a "small" effective ?
Reply 1: Thank you for your comment. As seen from Table 5, EBV group had more re – interventions than LVRS and also more EBV patients had at least 1 re-intervention than LVRS counterparts. The risk by time was not different which simply means that 1 event does not lead to a second event and the events are separate. Could we kindly ask if you could specify a bit more what exactly the question is?
Changes in text 1: Re-intervention differences were better explained in the Results section, Page 11, Paragraph 6, Lines 246-247 and in the Tables section, Table 5, Page 27.

Comment 2: - how do you treat pneumothorax after ebv ?
Reply 2: This is a valid and comment and we thank the reviewer for this. This has already been answered after the comments from another reviewer. Out of 7 pneumothorax patients, 4 had to have a new chest drain inserted and this is now considered as a re-intervention as per the comments of the other reviewer. We hope you agree with the request to consider the insertion of a drain as a separate re-intervention.
Changes in the text 2: Clarified in the Patients and methods section, Data subsection, Page 7, Paragraph 3, Lines 154-155 and in the Results section, Page 12, Paragraphs 7 and 10, Lines 255-256 and 263-265.

Comment 3: in MDT teams, ebv used to be done for patients with comorbidities ; your results confirm that there is no significant difference for operative follow up between "stronger" patients who underwent LVRS and "vulnerable" ones who will have EBV.
How many EBV finally have LVRS?
Reply 3: Thank you so much for this truly important comment. LVRS is a possibility after failed EBVs and in our cohort of patients 2 patients underwent LVRS following failed EBV intervention.
Changes in the text 3: Mentioned in the Results section, Page 12, Paragraph 7, Line 254.

Comment 4: comments :
- you may precise with is the butressed stapler material (Peristrip)
Reply 4: This is another valid comment. Buttressed material added in the text as per your comment.
Changes in the text 4: Mentioned in the Patients and methods section, Description of

interventions subsection, Page 6, Paragraph 1, Line 169.

Comment 5: - in the flow chart ; between the step with 99 patients and the constitution of 2 groups of 44 patients, you may put here the box of 11 patients excluded for missing data.
Reply 5: Thank you for your valid comment. Because these patients have been excluded before the cohort went into the propensity analysis, we have already added this before the 99 patients box if you would agree. If not then we will be happy to change this accordingly.
Changes in the text: None at this point.

Second External Peer Review

Review Comments

The authors made a great effort to answer the reviewers comment´s and to revise their manuscript accordingly. From my point of view the response is adequate and the paper has now substantially gained quality. Data and conclusions are now plausible and congruent. Some conclusions, which were not supported by the data have been removed and limitations of the study have been outlined better. All requested additional information in the methods and results section has been given.

I still regard this paper as highly original research (to my knowledge the first paper to directly compare LVRS and EBV, although in a retrospective manner), that contributes substantially to the field of lung volume reduction.