Peer Review File
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First round peer review

Reviewer A

The authors conducted a retrospective study to determine whether operative time of VATS anatomical resection contributed to the development of postoperative complications. They demonstrated that the operation time had been related to the development of postoperative complications and that multivariate analysis had identified factors to affect operative time.

Comment 1: The authors included benign pulmonary lesions as well as metastatic lung tumors. However, these cases are in the group without lymph node dissection which prolongs the operation time. Lymph node dissection has complications specific to itself such as AF. I think it is better to limit the subjects to primary lung tumor cases in order to align the backgrounds of the subjects and obtain more accurate results.
Reply 1: Thank you for this relevant comment. We totally agree and thus restricted our study population to patients with non-small cell lung cancer undergoing lobectomy or segmentectomy only. This will ensure higher homogeneity of the study population
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 2: Many of the factors included in the multivariate analysis were confounding variables. For example, the authors show in table 1 that BMI, FEV1.0, and Conversion thoracotomy are factors that have a strong effect on the operative time. When these factors are included in a multivariate analysis to reveals the development of postoperative complications, their p-values are generally attenuated. In such a case, not to perform multivariate analysis is one of the solutions. I'm afraid that the authors removed tobacco exposure from the multivariate analysis because it affected the expected results. The authors show in table 1 that tobacco exposure is strongly related to the operative time.
Reply 2: This is a very valid comment and we thank this reviewer for their constructive suggestion. We removed tobacco exposure from the multibariable analysis because it is a known confounding factor to a decreased FEV1, which we duly included in the multivariable analysis.
Changes in the text: None.

Comment 3: It is better to add intraoperative bleeding to the factors to be examined.
Reply 3: Due to the retrospective nature of the study, we did not have access to information pertaining to intra-operative loss of blood. That would have been an interesting data to analyze, but the nature of the study precluded us from including it.

We did mention this limitation in the text ("we did not analyze several intra-operative elements").
Changes in the text: We amended the discussion section to reflect this comment (Lines 218-220)

Comment 4: Is there any effect on the operative time and postoperative complications due to histological type?
Reply 4: We added this data to Table 2. Upon revision of the analysis, we found no association with pulmonary complications or length of operative time.
Changes in the text: see Table 2.

Comment 5: The authors should define a complex segmentectomy and show the case numbers before adding it to the analysis.
Reply 5: We agree with your comment and added the definition in our methods section.
Changes in the text: Definition of complex/simple segmentectomy was added in the methods section (page 5, lines 100-101).

Reviewer B

The author insisted that longer operative time can negatively affect patient postoperative morbidity, length of postoperative drainage, and postoperative hospitalization time. I totally understand these results because patients with longer operative time tends to have more comorbidities or lower preoperative pulmonary function, which can bring those worse perioperative results.

Comment 1: Thus, this manuscript has a serious problem like below:
Although this study included many patients, it had variety of patient background, which brought many biases. Moreover, the surgical procedures included segmentectomy, lobectomy, sleeve lobectomy, bilobectomy, and pneumonectomy. For example, comparison between segmentectomy and pneumonectomy was not reasonable because the invasiveness of the procedure and the candidate for the procedure were quite different. Even if this study used multivariate analyses, the author should focus on specific patient population at least about disease, tumor stage, and type of resection (ex. cStage1, NSCLC, lobectomy).
Reply 1: Thank you for your comment, we totally agree with your comment and adapted our manuscript and analyses with a better selected study population including only patients with non-small cell lung cancer undergoing segmentectomy or lobectomy. It is our experience that these two operations, bar any unforeseen complications or other major difference between cases, tend to last the same amount of time. Thus, we find them a relevant comparison.
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 2: The cut-off value of operative time was decided based on the "mean" operative time among all patients. However, "median" value is considered better.
Reply 2: We agree with this methodological comment. In the case of our study population, the median duration is 141 minutes. However, for the sake of clarity and simplicity, we preferred to use the cut-off of 150 minutes, which corresponds to a duration that most surgeons in our department consider acceptable for these surgeries.
Changes in the text: We have removed the mean and switched to the median.

Comment 3: The author described "we did not observe a significant association between conversion thoracotomy and postoperative morbidity in the multivariate analysis" in the discussion section. Please explain why this result happened.
Reply 3: Conversion thoracotomy was associated with increased morbidity in univariable analysis (HR 2.44). Surprinsigly, in multivariable analysis, the HR remained elevated at 1.62, without reaching the level of significance that would make it noteworthy (p=0.174). We can only hypothesize as to which reasons would explain this fact, but they span from purely methodological ones (confounding factors, small study population, etc) to more fundamental ones (direction of the correlation, etc). Whilst we do not have a clear-cut explanation, it is interesting to note that this finding might encourage surgeons to convert in cases of long or difficult operation, knowing that this decision might not jeopardize post-operative outcomes unduly.
Changes in the text: None.

Reviewer C

Comment 1: Forster and colleagues present a retrospective series on surgical time and postoperative morbidity. The main conclusion of the study is an association of longer surgical time with a higher postoperative morbidity. A finding which has often been reported and most likely is due to a negative confounding and/or selection bias as there is a selection of surgically uncomplicated cases due to factors which are not measurable which lead to longer surgical times and also complications.
Reply 1: We agree that this is the main limitation of such study. We also note that our results seem to corroborate this impression.
Changes in the text: We added a sentence to mention this limitation in the discussion section.

Comment 2: What is a short surgical time? The authors choose a cut off at 150 minutes (which I consider very long, my uncomplicated lobectomies usually take between 45 and 90 minutes skin to skin). Why and how was this cut-off chosen? Would „long" surgical time also be an independent risk factor if the cut-off was at 120min? 90 min?
Reply 2: As described in our methodology section, we chose a cut-off of 150 minutes based on our median operative time of 141 minutes (we rounded the cut-off to the next round number) and general experience of our surgical team. Our study included all segmentectomy and lobectomies for NSCLC performed by VATS. Simple and

complicated case were included, which can explain our median operative time higher than this reviewer's. Moreover, since this study was performed in a university center, teaching is frequent and operative time might be extended for that reason. Unfortunately, we did not have any data on teaching available in the files that we were allowed to review, but a further study might be interesting.
Changes in the text: No change.

Comment 3: The authors include VATS sleeve resections, complex segmentectomies and pneumonectomies which all are very challenging and far longer operations than a „simple" lobectomy. These surgeries should be excluded from the analysis or analyzed separately.
Reply 3: Thank you for your comment, we totally agree and adapted our manuscript and analyses with a more selected study population including patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only.
Changes in the text: Changes were applied throughout (manuscript and all tables).

Comment 4: Postoperative complications are not well defined and make interpretation even more difficult. They should be separated into minor and major complications (clavien dindo 1-2 and >2). Probably they should also be separated into cardiopulmonary and others (chylothorax, empyema, subQ emphysema…).
Reply 4: This is a very valid comment, and this design would be state-of-the-art for a prospective study. We did however run a retrospective study, and had to rely on the elements in the files that we were allowed to review. Because not all files were complete, or even as detailed as this reviewer would rightly expect, we had to settle for the smallest common denominator. This might slightly dilute the interpretation of our results, but it does not affect our general conclusions.
Changes in the text: No change.

Comment 5: After reanalysis the manuscript should be rewritten a little more rigourously: Why do you think a longer surgical time leads to more complications? What would make sense? Probably cardiopulmonary? Maybe wound infection? With the current mixing of surgeries and complications and the biasses resulting from the retrospective nature of this study and interpretations are extremely difficult.
Reply 5: We agree that the current design of our manuscript makes it difficult to draw detailed conclusions. We can only rely on educated assumptions, rooted in our vast clinical practice and observations. We did attempt to stay away from speculations, however, and to rely on evidence and all the data that was available to us, although we realize it is not quite as detailed as would be optimal. Please see also our previous response to the same reviewer.
Changes in the text: No change.

Reviewer D

This paper is very interesting because it investigated the relationship between

operative time and postoperative outcomes.
However, it is considered that the findings of this paper become ambiguous because of the method of selecting cases.
To clarify the core of this paper, please answer the following questions.

Comment 1: For example, lobectomy or segmentectomy, with or without lymph node dissection, with or without neoadjuvent therapy, and with or without conversion, etc. are clear that these factors have a direct impact on operative time and postoperative outcomes. Did the authors perform this study to determine trends in all cases undergoing VATS anatomical pulmonary resection?
We already know that cases with lymph node dissection take operative time longer than those without, and cases with conversion take operative time longer than those without.
Reply 1: We changed our study population and included only VATS segmentectomy and lobectomy for NSCLC. With this change, we did not observe a significant association between mediastinal lymph node dissection and operative time, but neadjuvant chemotherapy was on the other hand significantly associated. We performed this study in order to help identifying predictors of prolonged operative time in order to better prepare the cases et plan our daily schedule. As such, the underlying nature of the paper (by surgeons, for surgeons and rooted in clinical practice) should not be overlooked.
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 2: In addition, it would be more beneficial to exclude cases with "outliers". For example, I think it would be more informative to consider only "cases of primary lung cancer with lobectomy and lymph node dissection".
Reply 2: Thank you for your comment, we totally agree and adapted our manuscript and analyses with a more selected study population including patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only.
Changes in the text: Changes were applied throughout (manuscript and tables).

Reviewer E

Comment 1: The operation time is influenced by many factors. In this series, a lot of confronting factors influecned the operation time included neoadjuvant chemotherapy, sex, staging, primary lung cancer or nor, ect... Thus, the conclusion could not be made by current data.
Reply 1: We decided to restrict our study population to patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only. This excludes many outliers and strengthens our conclusions.
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 2: Please perfomr porpensity score matching for both groups of patients. Once both groups of patients were on the same condition, the role of operation time

could be evaluated more precisely.
Reply 2: This comment is very valid and we did consider the need for such preparatory work on the data. That being said, because the study populations are reasonably homogenous (see Table 1) in terms of comorbidities and type of surgery, perhaps especially so after we restricted our study population to patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only, we decided against this.
Changes in the text: No change.

Reviewer F

I congratulate the authors for the good outcomes observed in their series.
This study correlates operation time and postoperative morbidity.
I have several concerns related to the design and conclusions of this study.

Comment 1: This is a very heterogenous population that includes patients with benign diseases, metastatic disease and lung cancer. They should focus on one disease to reduce bias and increase discrimination.
Reply 1: Thank you for your comment, we totally agree and adapted our manuscript and analyses with a more selected study population including patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only.
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 2: The reason for the use of operation time as a binary variable is not clear to me. Why didn't the authors use it as a continuous variable and analyze outcomes with ROC curves and linear regression models?
Reply 2: This comment is methodologically correct and we thank this reviewer. On the other hand, the underlying general purpose of this paper should not be overlooked: it is a paper by surgeons, for surgeons, with a clear aim to help colleagues in the planning of the operative schedule. As such, whilst we understand that a clearer, more scientific definition of operative time might strengthen a more statistically-oriented paper, it was not its purpose. We rely on a wide surgical experience and do not need to plan by the minute. More likely, our aim is to roughly disentangle thoses case that will be more routine-like (thus "short") and predictably last under a certain amount of time, from those cases that will necessitate more time and resources ("long" operations), in a manner that the latter are ventilated over several days and not all planned on the same morning.
Changes in the text: No change.

Comment 3: Despite the results of the multivariable model there are many other confounding factors that were not taken into account as completeness of the fissure, vascular anatomic variations, position of the tumor (central vs peripheral), invasion of hilar structures and so on. Operation time is probably a surrogate of the combination of measured and unmeasured variables that interfere with time but are the real causes

of morbidity. So I challenge the correlation suggested in the final conclusion.
Reply 3: This comment is methodologically correct and we thank this reviewer. For this study, we faced various methodological challenges that make it less than optimal, although not entirely dismissable (in our view). These include elements discussed above (retrospective design, completeness of files, aim and audience of the study). All being said, the associations we observe are at least informative and as such, meet the primary purpose of our study. We nonetheless agree that this is a limitation in the sheer generalizability of our results, We mentioned it in the limitiations of the study.
Changes in the text: We added a sentence to mention this limitation in the discussion section.

Reviewer G

Random comment: I read and reviewed the manuscript from Forster et al. This study attempted to describe the impact of operative time on postoperative outcomes during VATS anatomic pulmonary resections. A threshold of 150 minutes was used to define short or long operative times.

Comment 1: This paper is challenged by the difficulty of correlation and causation when the question being asked is vague. As the authors note, increased operative time (OT) can reflect surgical complexity and prolonged OT has been associated with complications. Because these measures are significantly multifactorial and overlapping, observational associations alone are unable to answer specific questions and the data only serve to re-demonstrate known associations between patient/pre-operative factors and post-operative outcomes.
In the initial analysis, multiple factors known to be associated with postoperative morbidity (increased BMI, history of tobacco exposure, decreased FEV1/DLCO) are associated with increased operative time and thus the correlation between increased OT and postoperative morbidity could be anticipated but cannot be attributed specifically to the length of an operation. Moreover, within the multivariable analysis of factors associated with prolonged OT none of these preoperative patient factors is suggested to influence operation length, even though they are associated with increased 30 day mortality.
I would caution the authors not to use these findings to suggest that prolonged OT alone is a factor that should be predicted and managed as a means to prevent postoperative complications (line 172, 212-213). At best, the association is correlative (even if statistically significant) to other factors previously shown to be associated with increased postoperative complications and is therefore not novel.
Reply 1: Please kindly refer to Reviewer F, Reply 3, Reviewer C, Reply 4 and Reviewer D, Reply 1.
Changes in the text: See above.

Comment 2: As written the manuscript is not hypothesis driven, but is rather couched as an observational study (line 66-67). Restructuring the paper with a specific

hypothesis that can be tested with the data and then used to discuss changes in practice in the discussion may be helpful to the authors to create a more engaging topic. These ideas are hinted at throughout the manuscript; an OT threshold may prompt conversion to a thoracotomy and improve outcomes (Line 59). Similarly, an OT threshold may aid in 'operative efficiency' with a potential benefit to surgery service costs (Line 59), but are not pursued. These examples would be extremely challenging to study or implement and would be controversial, however, having a central (potentially provocative idea) would strengthen interest and, more importantly, would focus analysis of the data around support of a specific claim.
Reply 2: This reviewer is correct that our study is practical and observational. Whilst their suggestion is methodologically flawless and would make for a more scientific paper, it would however defeat our primary purpose, which was to share surgical practices with practitioner colleagues and contribute to the decision-making processes of the daily management of a surgery team.
Changes in the text: None.

Comment 3: The use of non-subject specific literature to discuss the data and support arguments should be avoided. Line 177-181, increased operative time was associated with increased infection risk but infectious complications as related to operative time in this study are not examined (theoretically they could be included under 'any adverse event influencing patient management,' but is not defined). Lines 214-216, while this study served to identify factors associated with increased operative times the differences between a thyroidectomy and lobectomy make this a less than apt comparison.
Reply 3: Thank you for this relevant comment. We agree and thus removed the non-subject specific literature.
Changes in the text: 4 references were removed (19-22 of this initial manuscript).

Comment 4: The breadth of pulmonary resections are now performed using a minimally invasive approach, however, there are significant differences in the difficulties and lengths of different operations. A sleeve left upper lobe resection is understood to take more time than a superior segmentectomy with advantageous anatomy. Did the authors consider limiting their analysis to a more uniform sample (just lobectomies for instance) and if not, what was the rationale?
Reply 4: Thank you for your comment, we totally agree and adapted our manuscript and analyses with a more selected study population including patients with non-small cell lung cancer undergoing segmentectomy or lobectomy only.
Changes in the text: Changes were applied throughout (manuscript and tables).

Comment 5: Could you confirm that patients only received neoadjuvant chemotherapy vs neoadjuvant chemoradiotherapy in your methods?
Reply 5: Yes, we confirm that it was only neoadjuvant chemotherapy.
Changes in the text: No change.

Comment 6: Lines 152-155: The breakdown of complications prompting readmission should be added to table 1 and separated by short and long OT group.
Reply 6: Thank you for your relevant comment. We added the data in our tables.
Changes in the text: Changes were applied in table 1.

Reviewer H

Authors performed VATS anatomical pulmonary resections for a pulmonary pathology and retrospectively evaluated their data to determine the impact of operative time on the development of post-operative complications after VATS anatomical resection. And they concluded that an operative time over 150 minutes is an individual risk factor for postoperative complications.
I would like to suggest some points to improve this paper.

Comment 1: (line 48)
VATS
---> Video-Assisted Thoracic Surgery (VATS)
Reply 1: We applied the change you proposed.
Changes in the text: We applied the change you proposed.

Comment 2: (line 78-79)
operative time (OT)
---> OT
Reply 2: We applied the change you proposed.
Changes in the text: We applied the change you proposed.

Comment 3: (line 131)
sex ratio female/male
---> female/male
Reply 3: We performed the change in our manuscript as proposed.
Changes in the text: Removed “sex ratio” from line 123.

Comment 4: (line 179; 191; 207; 214; 217)
104’632 ; 47’960 ; 20’565 ; 3454 ; 19’337
---> 104,632 ; 47,960 ; 20,565 ; 3,454 ; 19,337
Reply 4: We performed the change in our manuscript as proposed.
Changes in the text: See reply 4.

Second round peer review

Reviewer A

I understand that you have a lot of limitations because this paper is a retrospective cohort study, therefore you had to rely on the contents of the files that were allowed to review.
However, the association between "operative time" and "outcome or prognosis" that we truly wish to know is never the fact that "larger and more difficult surgeries for more advanced cancers take longer, have more complications, and have poorer prognoses", but “if surgery is performed under similar conditions, does longer operative time really lead to more complications and worse prognosis?”.
I would like you to carry out further refined research so that you can answer this proposition in the future.

Reply: This reviewer is correct and we take on their comment with gratitude. We already have plans to carry out future research as they suggest and will keep their comment in mind when implementing them.

Changes in the text: None.

Reviewer B

Focusing the analysis on a more uniform population (VATS lobectomy/segmentectomy for NSCLC) and adjusting the multivariable analysis improves the study.
Two major issues remain.
First, while it is appreciated that this is a retrospective analysis, retrospective data can be reanalyzed using more appropriate methods and additional retrospective data can be obtained from other sources (alternative databases, chart review) to support or disprove critiques of a study and its arguments. The authors seemed resistant to pursuing these avenues (Reviewer E comment/reply 2, Reviewer F comment/review 2 and 3). If the data simply does not exist or is incomplete, it is difficult to support or defend posited conclusions.
Second, I would challenge the assertion that this observational study is generalizable or could be relied upon to guide practice or plan operative schedules (Reviewer F, comment/reply 2). From a methodologic standpoint, the confounders related to operative time (with the limited controls provided by multivariable analysis), incomplete variables (tumor location, intraoperative findings, etc.) and the nonspecific 150 minute threshold do not seem robust enough to nudge a surgeon towards a thoracotomy all else being equal. The judgement to start with a thoracotomy or convert early is often the right call, however, that assessment is highly individualized based on surgeon and patient factors and the specifics of the OR schedule are not usually a primary consideration.
With additional data, methodologies and contextualization, it is possible the authors could support the assertion that operative time specifically influences postoperative outcomes (independent of confounding preoperative variables) to a greater extent than complications related to a thoracotomy. At this stage, however, the relationship between

these variables is obscure and the manuscript does not inform or change practice.

Reply: We are grateful that this reviewer acknowledged our improvements in the study after their initial comments. We are all-too-keenly aware of the limitations in data and data access. These are the limits of a retrospective study and we did indicate this clearly. We nonetheless gratefully accept this reviewer's comment and amended the conclusions accordingly, so that no trace of doubt might remain.

Our experience is that, within our department and with our team, the type of observations we made actually helped us guide our operative practice and plan our operative schedule. In a way, this agrees with this reviewer's comment insofar as this was only "generalizable" to our own, or similar teams. We have been working as a team for many years, we have collectively gathered vast experience over hundreds of cases, we have reasonably standardized procedures as befits a large, university hospital and yes, to some extent, we have observed that some operations are bound to last longer and, when this happens, a non-negligible number of those will have more complications and poorer prognosis.

That being said, whilst this last observation indeed curtails the generalizability of our conclusions, we thought it interesting enough to, at the very least, inform colleagues of our observations. One of the main non-quantifiable aspects of these surgeries is the collective expertise and the surgeon's instincts, and we found that these also can be educated. This reviewer is, methodologically speaking, correct that many factors will confound the results, but ultimately, it seemed to us that operative time was one easy-to-measure metric that could be used as guidance and, perhaps, proxy for other post-operative metrics.

We have amended the text to clarify this point.

Changes in the text: We amended the conclusion of the abstract (line 43), Introduction (lines 54, 62, 64-65), Discussion (lines 162-163, 215-217, 228-231, 233, 235) to reflect the answer above.

Third round peer review

Reviewer A

Comment: Thank you for your multiple and thoughtful revisions.

At the end of the day, I do not think the study convincingly demonstrates that prolonged operative time is associated with worse outcomes in a way that addresses the multiple confounders inherent to the data. Many of the factors identified were not novel (it is understood that neoadjuvant therapy

and increased BMI are associated with both increased operative difficulty, complications, and operative time). The authors have found internal utility to help guide their own practice, however, based on the manuscript I am unclear how this would generalize to other systems based on the factors associated with prolonged operative time.

Reply: We thank Reviewer A for this new round of comments. We received them with gratefulness, only marred with some degree of puzzlement. We fully understand that all Reviewers, and this includes Reviewer A, work with the highest possible professional ethics. In that sense, we completely understand that this reviewer should carry out the review process with diligence. We, however, wish to underline as follows:

- Over the course of the initial review process, we addressed comments by no fewer than 8 reviewers, to the satisfaction of the great majority of them.
- Over the course of the second round of the review process, we further answered questions by two reviewers, likely people who felt that their initial comments deserved some further consideration. In particular, then-reviewer A asked us specifically to "carry out further refined research so that you can answer this proposition **in the future**" (emphasis added). We gratefully acknowledged this proposal and already have plans to act on it.
- It is thus puzzling that, after two rounds of review and satisfactory answers, this reviewer should again bring up the comment below, not least after thanking us for "multiple and thoughtful revisions". We note that his criticism, whilst not entirely unfounded, is not novel, not rooted in any changes we might have made in our text that could warrant a revision and not a new element to be considered.
- We feel like this reviewer is unnecessarily creating an obstacle by over-emphasizing a known limit of our paper, which we have openly acknowledged, discussed and described.
- Furthermore, we fail to see how we can satisfactorily address this last comment, perhaps because it contains neither a question, nor a constructive proposal to amend or improve our manuscript.
- As such, we ask that you kindly reconsider your decision to require major revision based on this comment. Alternatively, we would be grateful if you could issue a suggestion as to how you would find it appropriate to answer this comment.
- We are committed to the rules that govern academic publishing and only work with the highest possible ethical standards. We cannot, however, engage in endless exchanges on points that we have already addressed. We also kindly request to be given reasonable perspectives that our paper, the review of which you supervised over several weeks and two rounds of written Review&Comment, be published in your journal without unnecessary delays or difficulties.

Changes in the text: None.