Peer Review File

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Reviewer A

The article "VE/VCO2 slope Threshold Optimization for Preoperative Evaluation in Lung Cancer Surgery: Identifying True High and Low-risk Groups" (JTD-23-1292-CL) proposes to identify new thresholds risks for the VE/VCO2 slope to screen patients before oncological lung resection.
Beyond the clinical interest of the research, several elements raise some questions and major revisions.

General remarks:
Positive points:
the article is well written, the methodology is appropriate and the elements relating to ethics are respected. The quality of English seems correct to me at my level of expertise (accustomed to writing/reading but not native).
The state of knowledge in the introduction is concise and sufficiently supported.
Although it is a retrospective work the cohort studied is of interesting size (158 subjects). This has already been the subject of a previous publication (Kristenson et al. JTCVS open 2022) but the evolution of the research question and the processing of the data does not resemble double publication.
The description of the methodology for measuring outcomes follows the recommendations and allows reproducibility of the measurements.
The conclusions present a real clinical interest.

Limitations:

Comment 1: It seems to me that the validity of the ROC curve is reduced by AUC values whose values are quite low (<0.8) with a wide confidence interval, this point must be addressed in discussion.

Reply 1: We agree with you and have added the following text to our "Limitations":
Changes in text: Line 249-252. Fourthly, although we argue that using two thresholds are advantageous from a clinical perspective, the AUC values from the ROC analysis was moderate (AUC 0.70). This is not surprising and indicate that more factors than only the VE/VCO2-slope are of importance for the risk of post operative complications.

Comment 2: The number of patients included in different analyzes needs to be reported in the tables.
Reply 2:
Thank you for your comment. We have updated table 2 accordingly with the number (and frequency) of patients in each category.

Comment 3: A table of patient characteristics would be appreciated so that the reader can have a clear view of the cohort involved in this study.

Reply 3: Thank you for your comment. We have added a new table, table 1 including patient characteristics. This table includes spirometry-data and we have therefore included a paragraph in the methods describing the pulmonary functions tests included, and added two references.

Changes in text: Other tables are updated with new table numbers, previous table 1 is now table 2 etc. Line 121-126: Pulmonary function testing
Preoperative pulmonary function testing was performed and included static and dynamic lung volumes (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), total lung capacity and residual volume) and carbon monoxide lung diffusion capacity corrected for hemoglobin, DLCOc. Spirometry measures were expressed as crude values as well as percentages of predicted (pp).(14, 15)

Comment 4: It is easier to assess the quality of the ROC curves for readers in the form of a figure, a priori this is not a limit with reference to the recommendations to authors, but at a minimum they can be offered as supplemental data.

Reply 4: We agree with you and have added a new figure to the manuscript, figure 1, showing the ROC-curves for the different thresholds of VE/VCO2-slope.
Changes in text: Line 213: Presentations of AUC values from ROC analyses for different thresholds of the VE/VCO2 slope are presented in Table 4 *and in Figure 1*.

Comment 5: The risk analyzes within this cohort need to be cross-validated in future work in order to confirm the external validity of the VE/VCO2 slope thresholds used. The positive and negative predictive values are necessarily quite good since calculated within this cohort, external validity remains an issue to be raised in the discussion section.

Reply 5: We agree with you and have added this to the limitations section.
Changes in text: Line 243-244: Therefore, the thresholds generated from this study as well as their long-term implications needs to be validated in future cohorts.

Comment 6: The authors finally retain the following thresholds: VE/VECO2 slope 30-41. Does the value of 41 for the upper threshold in the ROC analysis imply a value > 41 or >= 41 ? I wonder to what extent choosing 30-40 would not be simpler and more relevant if the objective is future clinical utility. Especially since, as previously discussed, these thresholds need to be cross-validated in the future in external cohorts independent of this one. This is close to what is found in patients operated for colorectal cancer (>40.1). The thresholds of 10.0 and 20.0 ml/kg/min of VO2 have been rounded for clear and simple clinical use, perhaps the VE/VCO2 slope values would also require this? What is the authors' position on this point? (can also be discussed in "Implications and actions needed")

Reply 6: We agree with you. 40-41 are within normal measurement error range. We have

changed the sentence in the end of the section where we discuss our findings in relation to the previous literature and we now discuss the similarity in the high specificity threshold in this material compared to other studies (with a cut-off value of 40).

Changes in text: Line 305: Thus, a patient presenting with a VE/VCO2 slope above approximately 40 during preoperative CPET should be considered at particularly high risk of complications and may require additional peri- and post-operative care.

Detailed comments:

Comment 7: - Lines 60-61 ; “Several studies have shown that the VE/VCO2 slope may be a stronger marker for postoperative complications and mortality compared to peak VO2.(4, 5, 6).” be careful, unlike the first 2 references, reference no. 6 deals with the extent to which the VE/VCO2 slope can REINFORCE the predictive nature of VO2, but does not allow the authors to assert a superiority of the predictive character.

Reply 7: In reference nr 6, the authors describe that major pulmonary complications or death was twice as common in patients with a VE/VCO2-slope ≥35 than in patients with a VE/VCO2-slope <35 (26% vs. 12%, respectively, RR 2.22, P = 0.030). In contrast to the VE/VCO2-slope, having a VO2peak <20 as compared to ≥20 ml/kg/min was not discriminative for major pulmonary complications or death (20% vs. 9%, respectively, RR 2.22, P = 0.14)

Comment 8: - Lines 83-86; Regarding the participants, were all types of surgery included (thoracotomy, VATS, RATS)? if yes to specify in the characteristics of the population later in the results.
Reply 8: Thank you for your comment. VATS and thoracotomies were included but no RATS. We have updated the manuscript in the result section accordingly.

Changes in text: Line 178-182: Open approach and MITS techniques were used in 143 (90%) versus 15 (10%) of patients, respectively. No difference was found in the frequency of primary outcome based on these two surgical techniques (20% versus 16%, p = 0.70). No patient was treated with robotic-assisted thoracoscopic surgery.

Comment 9: - Line 169; “A threshold of 31 was derived when using the highest Youden value (0.31) for the ROC analysis.” ; so that the reader visualizes the analysis perhaps a figure would be relevant with AUC accuracy. Possibly if this is redundant with the results of table 3 consider a common figure.
Reply 9: Please see answer to comment nr 4.

Comment 10- Line 177-179; “The two thresholds derived from the VE/VCO2 slope values closest to a corresponding 90% sensitivity (lower threshold) and 90% specificity (higher threshold) were 30 and 41 respectively.” Does the value of 41 in the ROC analysis imply a value > 41 or >=41? (joins a previous question in the general remarks)

Reply 10: Please see answer to question nr 6.

Comment 11: Lines 206-207: “Also, using two thresholds compared to one threshold increased the overall model quality based on the AUC analysis.” although the validity of the model is improved, the AUC remains low, the authors should either provide a reference to affirm the strength of the AUC, or consider discussing this within the limits of their study.
Reply 11: Please see answer in question nr 1.

Comment 12: - Strengths and limitations: discuss the external validity of the results (need to be evaluated in future independent cohorts)
Reply 12: We agree with Reviewer A. Please see our answer to comment nr 5.

Comment 13: - Lines 288-291; “Specifically, exercise training has been shown to increase ventilatory efficiency (i.e., lowering the VO/VCO2 slope) for patients with heart failure or pulmonary hypertension.(27)” => literature exists on the effect of prehabilitation in patients with lung cancer, it is preferable to use references related to this population category rather than patients with heart failure. Furthermore, the data are discordant, which does not allow us to be certain that ventilatory efficiency can really be improved by prehabilitation ; which reinforces the need to screen patients with poor ventilatory efficiency

Reply 13: Thank you for your valuable comment. We have deleted the reference from the heart failure setting and added two references showing the discordance in the current research field. We have also added a reasoning regarding the need to refer patients with very high ve/vco2 slope to exclude PAH or right heart failure.

Changes in text: Line 325-329: However, previous data are discordant regarding if prehabilitation can increase ventilatory efficiency (i.e., lowering the VE/VCO2 slope) in patients awaiting pulmonary resection.(30, 31) High VE/VCO2 slope can be an indication of manifest severe comorbidity such as pulmonary artery hypertension or right heart failure and these patients should preferably be investigated with echocardiography preoperatively.

Comment 13: End of the manuscript; the authors present au STROBE Statement, but do not specify in the methodology of the article that the latter follows this statement.
Reply 13: We have added a sentence in the method section and added a new reference (the STROBE guidelines, von Elm et al Lancet. 2007).
Changes in text: Line 98-99: The principles stated in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative were followed.(11)

Reviewer B

It is interesting to note that VE/CO2 is used to predict postoperative cardiac complications in three subgroups of pulmonary surgery patients. It was also interesting to note that the study results showed that using three risk groups based on the preoperative VE/VCO2 slope was better than the traditional stratification into two risk groups. However, the study lacks

consideration of the clinical background of the patients.

Comment 14: The study does not provide data on postoperative risk if the patients had COPD or interstitial pneumonia, which would change the risk. The study also did not provide a breakdown of causes of death or pulmonary complications. Above those are crucial and fundamental problems

Reply 14: Thank you for this comment. First, we have added two new covariates to our adjusted logistic regression analysis; preoperative diagnosis of chronic obstructive pulmonary disease and percent predicted total lung capacity (corresponding to interstitial lung disease). This resulted in only minor differences in the adjusted values now updated in table 3. Secondly, we have added information about ppFEV when describing cohort characteristics, showing that no patient with GOLD class >3 (ppFEV1 <30%) and we add this in the limitations section. Third, we have added information regarding causes of death and pulmonary complications in the results section.

Changes in text: Table 3 updated with two new covariates.

Line 177-178: and ppFEV1…76 ± 19 % (range 30-124),

Line 184-189: Registered complications were pneumonia (n=9), pulmonary embolus (n=1), empyema (n=4), delayed extubation (n=5), re-operation (n=12), respiratory insufficiency (n=3). The causes of death in the three patients were: pneumonia and subsequently respiratory failure, sudden circulatory collapse (no autopsy performed but clinically massive pulmonary embolus was suspected), and the third patient suffered cardiac herniation with subsequent right heart failure following left sided pneumonectomy.

Line 245-249: Third, we were unable to include patients with a very high risk of complications (peak VO2 <10 ml/kg/min *or ppFEV < 30%*), as these patients did not undergo surgery at our center. Therefore, the thresholds proposed in this study are only valid when first excluding this very frail patient group. *This is important since patients with severe COPD can present with normal VE/VCO2 slopes due to their ventilatory limitation and/or altered set point for paCO2(20).*

Reviewer C

This manuscript presents an interesting research on the utility of the VE/VCO2 slope in risk stratification for patients undergoing lung cancer surgery.

While the scientific article is generally robust, there are some aspects in which I believe it could be improved:
Comment 14: Long-term Clinical Relevance: Although the article analyzes complications occurring during the first 30 postoperative days, it would have been interesting to determine if there are differences in terms of longer-term postoperative complication outcomes (e.g., the

first 90 days) rather than just the initial 30 days after surgery. Are there any long-term implications for these patients?

Reply 14: Unfortunately, we do not have data for follow up > 30 days. This is a retrospective study and the majority of our outcome data rely on the national thoracic surgery register that only includes in-hospital data. We have added this to our limitations section.

Changes in text: Line 242-244: Second, this was a single-center study with 30 days follow up time. Therefore, the thresholds generated from this study as well as their long-term implications needs to be validated in future cohorts.

Comment 15: Interpretation of Results: In addition to presenting the results, a more detailed interpretation of the findings and their potential impact on clinical practice could be provided. How should this information be used in decision-making? Additionally, reference could be made to possible future applications of this study and whether it might lead to additional research or future changes in medical practice.

Reply 15: Thank you for your comment. We have expanded the section “implications and actions needed”, please see below.

Changes in text: Line 318-321: First, although the frequency of the primary outcome was 47% in the high-risk group identified, this patient group still had a low risk of short term mortality and should not be excluded from surgery only based on this finding. Instead...

Comment 16: Updated References: While the article mentions previous research, some of the references are relatively old (e.g., from the 1990s). It would be useful to include more recent research that can support or complement the study's findings.

Reply 16: We agree with you that some of our references are quite old. However, as we mention in the section comparison with similar research, VE/VCO2 slope determination was first used by cardiologists evaluating patients with heart failure. Therefore, most studies using CPET for preoperative risk stratification refer to thresholds of VE/VCO2 slope generated from historical data in heart failure patients in the 1990s or early 2000s. Therefore, studies like the current are required in order to re-evaluate and update these (old) thresholds.
Changes in text: We wish to keep these references.

Reviewer D

In their retrospective study, the authors analyzed the value of new thresholds of VE/VCO2 slopes for predicting major pulmonary complications after anatomical resections for lung cancer.
The authors obtained IRB approval for the study. The study is reported according to the STROBE guidelines. The manuscript is written in a clear and understandable manner. The

English language quality is very good. Introduction gives sufficient background for the study. Methodology is correct. Results are presented clearly. Discussion is thorough, the authors refer the obtained results to the current literature. Information presented in tables supports the results. The study is of great clinical value and may be useful to thoracic surgeons involved in the treatment of lung cancer. I don't have any major comments. Once again, congratulations on a very interesting study.

Reviewer E

The authors have undertaken a retrospective analysis on a cohort of 158 lung cancer patients who underwent either lobectomy or pneumonectomy. In doing so, they have elucidated the optimal thresholds for the VE/VCO2 slope derived from CPET as a prognostic indicator for predicting major pulmonary complications (MPC) or mortality post-surgery. Importantly, they delineate two distinct thresholds: ≤30 and ≥41, which facilitated categorizing patients into three discernible risk groups. Subsequently, there was a notable variance in complication rates among these groups, with incidences being 5%, 16%, and 47% respectively ($p < 0.001$).

The manuscript is cogently written and offers tangible clinical insights into predictors for postoperative complications following lung resection. As proposed by the authors, the stratification into three risk groups stands out for its potential to discriminate between high and low-risk patients while concurrently identifying those of moderate risk.

In the discussion, the authors have appropriately referenced essential prior literature and have adeptly deliberated on their study's limitations and strengths, showcasing a comprehensive understanding of their findings in the broader context of existing research. Such a classification would undoubtedly be a valuable tool in clinical decision-making, enhancing patient care and postoperative management strategies.

Given its relevance, depth, and methodological rigor, I believe this paper is indeed worthy of publication.