

Peer Review File

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Reviewer A

Thank you for submitting your work to the Journal of Thoracic Disease.

Major comments

1-In this study, Leicester Cough Questionnaire (LCQ) was used in order to predict postoperative complication in patients who underwent major lung resection. However, LCQ was developed for evaluating quality of life in patients suffering from cough, whose primary object is far from the prediction of postoperative complication. If your study is intended to have a rationale, at least, study subjects should be confined to those suffering from cough, so should postoperative complications be cough-related ones. Meanwhile, study subjects and postoperative complications were not sufficiently described in the study.

Reply 1

Thank you for your comment. The LCQ was developed to measure the quality of life of patients suffering from chronic cough. Patients who undergo lung surgery often have a smoking history, chronic obstructive pulmonary disease (COPD) and/or pulmonary cancer, which can lead to chronic cough. Patients who had no cough at all were instructed to check the maximum quality of life (7) for all questions, since all questions of the LCQ are related to the cough. Our idea was to assess whether cough can impact the risk of postoperative complication, but defining cough as a binary variable (Yes/No) would not distinguish severe cough from minor cough, which would reduce the predictive performance. Excluding patients with no cough at all, would generate a selection bias excluding potentially patients with low risk of complications, underestimating the predictive performance of cough.

Cough-related post-operative complications are hard, if not impossible to identify, because without and with cough, the same complications are possible. For instance, how can we know that an atelectasis complication is related to the cough or not? Moreover, for statistical power considerations, as the sample size was not large, using all complications could increase the number of events, therefore, the statistical power.

Changes in the text:

We added the type of major lung resection (lobectomy or segmentectomy), disease (cancer, emphysema, ...) as well as the TNM stage (since almost all patients had pulmonary cancer) in Table 1. We described postoperative complications in Table 4.

2. Although this study was retrospective, the time points of variable parameters including LCQ, QLQ-LC13, PF, and CPF need to be described concretely in METHODS and/or RESULTS.

Reply 2:

Thank you for your comment.

We provided more concrete descriptions of the conditions under which the questionnaires and PF were conducted in the METHODS section.

Changes in the text:

Page 4, line 117 to 120: "The QLQ-LC13 questionnaire was given to the patient along with the LCQ questionnaire on the day before the surgery in their hospital room. For patients arriving on the day of their surgery, the questionnaires were completed approximately two or three hours before the procedure in the outpatient surgery department. Patients filled out the questionnaire independently.

Page 5, line 128 to 129:" The PF measurements were taken before the patients completed the

questionnaires.

Reviewer B

Corbice and colleagues investigated the utility of Leicester Cough Questionnaire (LCQ) for predicting postoperative complications after major lung resection in 70 patients with non-small cell lung cancer (NSCLC). The results were unfortunately negative.

Major comments

1. First of all, the number of studied subjects is too small to draw a definitive conclusion, especially when the results were negative.

Reply 1

Thank you for your comment.

We agree with your comment, this problem was already mentioned in the text.

Page 14, Discussion, line 306-307. « The small sample size limits the power of the study, so we cannot draw a definitive conclusion from negative results ... »

Page 15, Conclusion, line 329-330: « However, the statistical precision is insufficient to exclude the existence of a moderate predictive capacity. ... »

Change in the text:

We added the sentence « The small sample size limits the power of the study, so we cannot draw a definitive conclusion from negative results.» in the Limitations section of the Discussion.

2. The rationale of the study: Why did the authors consider that preoperative LCQ could be a predictor of postoperative complications? It might merely reflect the preoperative status of already existing pulmonary (and also cardiac etc.) diseases including NSCLC which is to be resected.

Reply 2:

Thank you for your comment. Although many prognostic factors are known in pulmonary surgery, cough is under-evaluated and there is little literature on it. We hypothesized that cough could induce complications, such as prolonged air leak, but causality is not our primary aim. Indeed, we hypothesized that assessing cough pre-operatively could better inform the surgeon on the risk of complications, even if part of this information is due to the fact that the cough is indicative of a poor pulmonary status.

3. Why did the authors evaluate cough peak flow (CPF) as a comparator of LCQ? CPF examines neuromuscular activity and the strength of coughing as a defensive mechanism against secretion retention and aspiration leading to infection.

Reply 3:

Thank you for your comment.

Prognosis of patients with COPD can hardly be interpreted without an objective measurement of the obstructive syndrome. Cough may be correlated to the COPD status but completely ignoring the obstructive syndrome severity could lead to an overoptimistic interpretation of the predictive value of cough alone. Our population has no neuromuscular disease, COPD being the primary reason for reduced peak flow.

Change in the text:

In the introduction, we added a few words of rationale:” We also assessed the utility of the Quality of Life Questionnaire for lung cancer 13 (QLQ LC13), peak flow (PF) and cough peak flow (CPF) to predict postoperative complications as they are objective measurements of the obstructive syndrome that may be correlated to the subjective cough.”

Major comments

1. Quality of English needs to be extensively improved by native English editors.

Reply 1.

Thank you for your comment.

The new manuscript has been edited by a native English speaker.

Reviewer C

In this retrospective cohort study the authors analysed to what extent the Leicester Cough Questionnaire predicts postoperative complications after major lung resection.

The study is interesting, but in my opinion there are numerous points that need explanation:

Abstract:

1. It is unclear if only patients with NSCLC were included in this study. If it is true, at least clinical stage of the disease is an important factor to add to better characterize the population.

Reply 1:

Thank you for your comment. All patients with major pulmonary surgery (NSCLC, volume reduction, etc.) were eligible although most patients were operated for NSCLC. We clarified our intent in the BACKGROUND section of the abstract and the start of INTRODUCTION because they were misleading, as they were too focused on NSCLC (main indication). The new wording make it clearer that all major surgeries are taken in account. Moreover, we had specified in the methods section of the abstract that any major pulmonary surgery could be included on page 1, lines 24 to 26. We further clarified these criteria: “The inclusion criteria were patients aged ≥ 18 years who underwent major lung resection for any indication”

Change in the table: The surgical indication, type of resection, and TNM stage, for the subgroup of patients with NSCLC, have been added to the general description of patients on page 6, Table 1.

2. I understand that AUC was used to analyze if LCQ may predict presence (1) of absence (0) of post-surgery complications. If not, it should be explained more precisely). The AUC ROC measures the degree of separability (here the diagnostic accuracy), not the correlation. Thus, the first sentence of conclusion should be modified to be more precise.

Reply 2:

We had used the term “correlation” as a generic statistical describing the “dependence” of two variables, i.e. the distribution of a first variable conditional to the second is dependent on the value of the second variable. However, we acknowledge that this term is ambiguous, therefore we replaced all occurrences of this term by “predictive capacity” for area under curves, and reserved the term “correlation” to Spearman and Pearson correlation coefficients between two quantitative variables.

3. What should be the sample size of the study to identify the moderate correlation between pre-surgery LCQ and duration of the hospital stay or of severity of the complications? Generally speaking, the lower the expected correlation is, the higher is the sample size. The same for estimation of sample size for AUC.

Assuming a moderate correlation ($R=0.30$) between the pre-surgery LCQ and the duration of hospital stay, a two-sided type I error rate at 5% to compare this correlation coefficient to zero, a sample size of 85 patients was needed to get a statistical power at 80%, which is slightly higher than our sample size.

Assuming a complication rate at 30% (observed rate 27.1%), a moderate area under ROC curve ($AUC = 0.70$) for prediction of post-operative complications by the pre-surgery LCQ, a two-sided type I error rate at 5% to compare this AUC to 0.50, a sample size of 65 patients overall would have been enough to get a power of 80%.

For a weak predictive power for post-operative complications ($AUC = 0.65$), the sample size required for 80% power would have been 125 patients overall.

We added a “SAMPLE SIZE CALCULATION” subsection to the METHODS section.

Introduction:

1.Aim of the study: Assuming that all patients were lung cancer patients in I-II stage, why the authors choose LCQ, if majority of patients did not complain of cough? Instead, QLQ-LC13 seems to be better than LCQ.

Reply 1:

Thank you for your comment. The included patients were aged over 18, had undergone major lung resection, and had completed the LCQ. Not all patients in our cohort had lung cancer (Table 1, page 6). Patients with stage I or II cancer may indeed have a history of conditions such as COPD, asthma, or other chronic respiratory diseases, thus experiencing chronic cough. The QLQ-LC13 is designed for cancer patients. As we aimed to assess the predictive power of cough on the risk of complications, the LCQ was suited to our objective.

2.In study by Wu et al. (Curr Oncol. 2022) LCQ was used to measure cough 2 and 6 weeks after surgery, while type of surgery was the factor influencing on presence of postsurgical cough.

Reply 2:

Thank you for your comment. The primary objective of the study was to assess whether cough is predictive of post-operative complications; after surgery, prediction is not relevant anymore. The presence of postsurgical cough is an interesting research subject, but it is not the same research subject.

3.Had all patients (even those who did not cough) cough peak flow measured?

Reply 3:

Thank you for your comment. Pulmonary function tests were conducted on all 70 patients in the cohort. Change in the text: We have specified this information on page 6, in the Results section, line 167-168: "The measurement of PF was performed on the 70 patients in the cohort"

4. Did patients agree for using their data for this study?

Reply 4:

Due to the retrospective nature of this study, the specific consent to this specific study was not obtained. However, in our center, all patients are informed that their health data may be used for future retrospective research studies. They have the possibility to oppose to this data re-use if they wish.

Change in the text:

We added a "PATIENT CONSENT & ETHICS" subsection of "MATERIALS AND METHODS".

Materials and methods:

1.Please add list of complications and the Clavien-Dindo classification.

Reply 1:

Thank you for your comment.

Changes in the text:

Complications have been added to Table 4 .

The Clavien-Dindo classification is in appendix 1.

2.Why only 71 patients from 201 were included? Where there any exclusion criteria?

Reply 2:

Thank you for your comment.

The inclusion criteria were to be 18 years or older, have undergone major lung resection, and have completed the LCQ questionnaire. Inclusion criteria are described on page 3, in the Eligibility paragraph. We clarified reasons of exclusion in an updated flow chart: most patients were excluded because they had not completed the questionnaire. Moreover, we added a paragraph in the discussion explaining why the questionnaire was not filled for all patients: Page 14 Line 305-308: "The reason for including only 71 of 210 patients in the study was not due to patient characteristics but rather to the organization within the department. These patients did not fill the questionnaire. Only one caregiver was responsible for collecting the questionnaires, and some outpatients were difficult to reach".

3. Please add information about the sample size of the study to analyze the AUC for the main goal.

Thank you. As we already told you, we added a “SAMPLE SIZE CALCULATION” subsection to the METHODS section.

4. As some results are given as mean +/- standards deviation and Pearson correlation coefficient was measured, did data had normal distribution?

Obviously, LCQ scores, DLCO and FEV1 do not have normal distributions because they are bounded, but normality is not mandatory to compute means and standard deviations. Outliers may severely influence means or standard deviations, but with LCQ, DLCO and FEV1, there are no outliers, since these distributions are bounded. Due to the central limit theorem, on moderate to large sample sizes, the sampling fluctuations of Pearson’s correlation coefficient can be approximated to a normal distribution, especially if there are no outliers. The quality of approximation of the variance calculation of Pearson’s correlation coefficient is known to be very good when the correlation is close to zero, which is observed for almost all our correlations.

We think that this discussion is too technical to be worth adding to the manuscript.

Results:

1. Please add data concerning indications for lung surgery; if it is lung cancer - stage of the disease.

Reply 1:

Thank you for your comment.

Change in the text: The TNM stage has been added to Table 1, for patients with cancer.

2. Table 2: what kind of cardio (mio)pathy was diagnosed? Did the authors mean heart failure?

Reply 2:

In some cases, it involves ischemic heart disease with or without cardiac failure, while in others, it concerns cardiac rhythm disorders with or without cardiac failure.

We think that, as this is not the primary research subject, we do not need finer details about the cardiopathy.

3. In Table 4 there is distribution of severity of complications, but there is no information about type of complications.

Reply 3:

Thank you for your comment.

Change in the text: Complications have been added to Table 4.

4. Please add p- vale, when AUC ROC is reported.

Thank you for your comment.

We added P-value comparing AUC to 0.50 to figures & text.

5. Please verify if is a correlation or AUC between LCQ and presence of post-operative complications ≥ 2 (line 212-213)

Thank you for your comment. This sentence was redundant with lines 203-204; therefore we removed it.

6. Please check if sentence in line 223-224 refers to correlation or AUC.

Thank you for your comment. It is AUCs; we now use the term “predictive capacity” rather than correlation.

7. As patients had spirometry and DLCO, what were AUC for FEV1, FVC or DLCO in predicting postoperative complications?

The DLCO had an AUC estimated at 0.74 (95% CI: 0.62 to 0.86, p=0.003); the FEV1 was at 0.72 (95% CI: 0.59 to 0.86, p=0.004).

However, as the predictive performances of DLCO and FEV1 are well known, we did not show these predictive performances in the study, but we estimated whether cough could provide predictive information in addition to these variables in the multivariable model.

If the editor thinks that these two AUCs calculations are important, we may add them to the manuscript.

Discussion:

1. Line 241- 242 and 243-244: Did authors mean correlation or AUC?

Reply 1:

Thank you for your comment.

We now use the term “predictive performance” for AUCs.

2. Line 253-257: It is simplification to assess prevalence of cough based on LCQ in patients with newly diagnosed lung cancer. Even if their LCQ is high, they might have cough as they are frequently smokers (Dicpinigitis PV. Effect of tobacco and electronic cigarette use on cough reflex sensitivity. Pulm Pharm Ther 2017)

Reply 2:

Thank you for your comment. Indeed, this indicates only impaired quality of life related to cough rather than any chronic cough. Therefore we removed the sentence “*This corresponds to the prevalence of chronic cough among future thoracic surgery patients*”.

Reviewer D

Thank you for giving me the opportunity to review this manuscript. This article examined whether the chronic cough questionnaire had any relevance in predicting postoperative complications of lung surgery. This study revealed that the questionnaire was not useful in predicting postoperative complications of lung surgery.

The idea is original, and the prevalence of chronic cough in preoperative patients with thoracic disease seems to be clear. However, it was not predictor of postoperative complications because the questionnaire for chronic cough was used, and it is difficult in this study to discuss the relationship with studies of postoperative cough.

Reply 1:

Thank you for your comment. We observed that this tool was not predictive of postoperative complications. Since there were no other studies in this specific context, our discussion relied on studies that evaluated postoperative cough. Postoperative complications may be difficult to assess with a preoperative questionnaire, since they are likely to be largely influenced by the surgical procedure.

Reply 2:

Thank you for your comment. We agree with your observation. Complications are influenced by factors such as the type of resection, surgical approach, intubation duration, and peritracheal lymph node dissection, as you mentioned. However, postoperative complications are also influenced by the patient's baseline condition, including their results in pulmonary function tests, measurement of VO2 max, and field tests.

It would be interesting to characterize those who do not have a chronic cough preoperatively but have a postoperative cough. In the literature cited, this seems to be more common after peritracheal lymph node dissection. (Mu T, et al. Ann Thorac Surg 2023; 115:1337-43.)

Reply 3:

Thank you for your comment.

Indeed, it would be interesting to assess both preoperative and postoperative conditions, as we mention at the end of the discussion page 15 line 326 to 328: “Therefore, it would be pertinent to investigate the

impact of this post-operative cough in patients undergoing major lung resection, on post-operative complications such as the duration of pleural drainage, the occurrence of subpleural emphysema, and the length of stay.

Reviewer E

Thank you for your study into the association of LCQ, lung cancer health status, peak flow and peak cough flow (PCF) with post-operative complications in lung cancer. I have a few comments.

Major

1. Is cough as a symptom associated with post-operative complications in lung cancer? If so, it would make sense to investigate LCQ's association with post-operative complication. LCQ is a cough-specific health status. By extension, a hypothesis of LCQ being associated with complications would not be logical a priori if cough was not associated with complications. I struggle to see the a priori to lead to a hypothesis to investigate LCQ in this context.

Reply 1:

Thank you for your comment.

Chronic cough is not associated with postoperative complications. Here, we are not exclusively focusing on patients with lung cancer, but on those undergoing major lung resection. We aimed to evaluate chronic cough in our patients to determine if its presence preoperatively had an influence on the risk of postoperative complications. Chronic cough is a symptom affecting 10% of the global population with an impact on quality of life. As mentioned at the end of the discussion, lines 323 to 324, the occurrence of postoperative cough is in the range of 25 to 50%.

2. The authors quite correctly noted that the LCQ total score was only below the normal threshold in a small number of patients. This finding can certainly explain the lack of association observed with complications. It once again can simply reflect on the a priori as described in my previous comment.

Reply 2:

Thank you for your comment.

We observed in our results that only 21.4% of our patients experienced a reduction in their quality of life related to chronic cough, despite their history of smoking, respiratory background, and the current status of their illness.

3. I am not certain why one would look at any association between pre-operative LCQ with duration of pleural drain and duration of hospitalisation. What would be the rationale for any associations in terms of physiology and mechanism?

Reply 3:

Thank you for your comment.

In the postoperative period, the occurrence of cough is in the range of 25 to 50%. It is common for patients to have pleural leaks or "bubbling" only when coughing, quantified through thoracic drain outputs. When our patients experience this situation, pleural drainage continues, and the thoracic drain is only removed when there is no more leakage, both at rest, during mobilization, and with coughing. Therefore, if the patient has a cough that leads to pleural leaks, their drainage duration is extended, consequently prolonging their hospitalization.

4. Meanwhile, I can understand QLQ-LC13 and peak flow as potential predictors of complications. On the other hand, PCF is unlikely to be reduced unless there was neuromuscular disorder or airflow obstruction. I suspect the former is unlikely in a surgical lung cancer cohort, thus once again I do not see the rationale for the hypothesis to investigate PCF.

Reply 4:

Thank you for your comment.

PCF help assess whether a patient will have an effective cough. If their PCF is less than 270 L/min, there is a risk of inefficiency. Our patients often have an obstructive syndrome (such as COPD or asthma), which by definition involves a decrease in expiratory flow rates.

Page 14, lignes 297 to 304: « Regarding CPF, no studies were found on the preoperative use of CPF in patients with NSCLC. CPF has primarily been studied in patients with neuromuscular diseases and to predict the success of extubation in intensive care unit patients (30). Patients undergoing lung resection surgery experience a restrictive syndrome in the postoperative period due to the involvement of both the thoracic wall and lung parenchyma (31). Additionally, unilateral left vocal cord paralysis is a relatively common comorbidity in lung surgery (32). This surgery-related paralysis is associated with a higher incidence of aspiration pneumonia and extended hospitalization (32). It would be interesting to evaluate a worsening of preexisting cough in the postoperative period.»

5. The multivariate (MV) analysis is quite an interesting part, and it reiterates the difficulty in predicting post-operative complications. For example, P-Possum score has multiple variable for general surgery. Do the authors feel that a single parameter, i.e. LCQ, would have been predictive?

Overall, we think that predictive performance of single parameter models can be good if the variable is relevant and synthetic such as the sit to stand test (*Boujibar F, Gillibert A, Bonnevie T, Rinieri P, Montagne F, Selim J, et al. The 6-minute stepper test and the sit-to-stand test predict complications after major pulmonary resection via minimally invasive surgery: a prospective inception cohort study. J Physiother. 2022;68(2):130-5*); such good performance was not expected for the LCQ. However, multivariable models can provide non-negligible improvements over single-variable models. Since the primary objective of the study is to assess the predictive power of LCQ alone, we did not discuss that.

6. The discussion is quite long and there is a fair bit of repetition. It does not flow very well and meanders.

Reply 6:

Thank you for your comment.

We have removed lines 256/257, 262 to 264 on page 12, and lines 285 to 289 page 14.

Minor

1. I do not think that a CONSORT diagram is needed with the sample size and numbers involved.

Reply 1:

Thank you for your comment.

We chose to use a flowchart because it helps assessing a possible selection bias.

2. No need to state if it was Pearson or Spearman correlation in the results section once the statistical methods are justified in the relevant section.

Reply 2: Thank you for your comment. We think that Pearson and Spearman correlation coefficients are not the same, and that this redundant precision in the results section makes it easier to read the article without having to look back and forward from RESULTS to METHODS.

Reviewer F

Thank you for the opportunity to review your work looking into the predictive value of the LCQ on post-operative morbidity amongst other measurement such as PF and CPF.

I found this to be an interesting topic and commend you for this. I believe it is important to continue to predict patients at higher risk in order to fully inform patients on post operative outcomes as well as reduce risk.

Reply 1: Thank you for your comment.

There is no mention of the thoracoscore in pre-operative risk modelling and perhaps there should

be as it is a well known model for this.

Reply 2: Thank you for your comment. The dyspnea scores were not collected, and it was not possible to retrieve them retrospectively. We agree with your observation; it would have been valuable to have this data.

We added a mention to the thoracscore in the INTRODUCTION: “Cough is not systematically assessed in pre-operative setting of pulmonary resection and has not been used in multivariable risk prediction scores such as the Thoracscore.”

It would also be worth mentioning why there was such a large drop out 201 to 71 as patients were not eligible - the criteria was anyone over 18. Did they simply not fill in the LCQ?

Reply 3:

Thank you for your comment.

Patients who were not included had not completed the questionnaire. This is now shown clearly in the flow chart.