JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 3.005

Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-22-1156

Reviewer A

This study demonstrates some useful parameters for predicting post-operative complications of lobectomy. Given the careful collection of data the submission would be greatly strengthened by additional analyses.

1) Is there any differences between the lobe removed and the rate of complication? For example, certainly, one would expect RML to be associated with fewer complications.

Reply: We evaluated and analyzed the association between the location of lung cancer and postoperative complications (PPCs) after lung cancer surgery. However, there was no significant difference between the groups. Please, see Table 1 and Table 3.

2) Is there a difference in histology based complications? Adenocarcinoma vs squamous cell?

Reply: We evaluated and analyzed the association between histology of lung cancer and PPCs after lung cancer surgery. However, there was no significant difference between the groups. Please, see Table 1 and Table 3.

3) Although the authors state that smoking is a poor predictor, active smokers are known to have worse outcomes. Was there an attempt to define if there were active (current) smokers?

Reply: We absolutely agreed the Reviewer A's comment. We re-evaluated smoking history. We got the result that smoking was one of risk factors for PPCs. We added it in Results.

Reviewer B

The authors reviewed the results of elderly patients undergoing lobectomy for lung cancer and found that low preoperative FVC, low FEV1, and low skeletal muscle mass were associated with postoperative complications. They concluded that skeletal muscle mass is a useful predictor of postoperative complications in patients undergoing lobectomy for lung cancer.

1) Skeletal muscle mass varies between men and women, and the definition of sarcopenia usually varies between men and women, but this has not been taken into account.

Reply: We absolutely agreed Reviewer B's comment. As we described in Discussion, sarcopenia has been defined as cross-sectional area (CSA) of the specific muscle indexed with body surfaced area less than median and its value was different according to sex. However, a consensus definition of sarcopenia has not been established. The European consensus statement recommendations are based on

healthy young adults. Therefore, we evaluated just CSA, not the existence of sacropenia. However, the evaluation from larger population for association between sarcopenia defined by age, sex and individual activity and PPCs after lung cancer surgery might be helpful.

2) According to various evidence to date, the standard preoperative assessment is considered by current guidelines to be ppoFEV1 and ppoDLCO, plus assessment of exercise tolerance (with the Stair Climbing Test or CPET). I do not believe that FVC and skeletal muscle mass are at all superior to these, which the authors claim are better preoperative assessments that predict more complications.
(Brunelli A, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e166S-e190S.)
Reply: Traditionally, predictive postoperative (ppo) values of pulmonary function test (PFT), especially forced expiratory volume in one second (FEV1) (ppoFEV1), or diffusing capacity of lung for carbon monoxide (DL_{CO}) (ppoDL_{CO}) has been regarded as the most reliable predictor for PPCs after lung cancer surgery [Forster C, et al. Is faster better? Impact of operative time on postoperative outcomes after VATS anatomical pulmonary resection. J Thorac Dis 2022; 14: 1980-9., Brunelli A. Preoperative functional workup for patients with advanced lung cancer. J Thorac Dis 2016; 8: S840-S8.]. However, the process of ppoFEV1 or ppoDL_{CO} is not simple or intuitive because the formula for ppoFEV1 or ppoDL_{CO} requires the number of functional remained segments after lung cancer surgery or normal value of FEV1 or DL_{CO} for individual patient. Although the association with skeletal muscle mass, and ppoFEV1 or ppoDL_{CO} for predictability of PPCs was not evaluated in the present study, it might be helpful to confirm skeletal muscle as a predictor for PPCs. We added as following in Discussion. “Preoperative careful physiologic assessment is essential to identify the patient with risk of PPCs after lung cancer surgery and enable appropriate management immediately after the surgery. Preoperative physiologic assessment includes cardiovascular evaluation, PFT, diffusing capacity of lung for carbon monoxide (DL_{CO}) and so on. Traditionally, predictive postoperative (ppo) values of PFT, especially FEV1 (ppoFEV1), or DL_{CO} (ppoDL_{CO}) has been regarded as the most reliable predictor for PPCs after lung cancer surgery. However, the process of ppoFEV1 or ppoDL_{CO} is not simple or intuitive because the formula for ppoFEV1 or ppoDL_{CO} requires the number of functional remained segments after lung cancer surgery or normal value of FEV1 or DL_{CO} for individual patient. Although the association with skeletal muscle mass, and ppoFEV1 or ppoDL_{CO} for predictability of PPCs was not evaluated in the present study, it might be helpful to confirm skeletal muscle as a predictor for PPCs.

3) 197 patients is a small number for the study, and this information is missing from the abstract.
Reply: The small population in the present study was one of limitations as we described in Discussion. We added the number of analyzed patients in Abstract.

JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 3.005

Reviewer C

I read with interest this article, describing pre-operative measures of skeletal muscle mass in 197 patients undergoing lobectomy for lung cancer, and studying its association with postoperative pulmonary complications.

Some issues need nevertheless to be acknowledged.

First, I am not sure that the article is written in correct English. For instance, I think that the word “elderly” should be used instead of “older”, but English is not my native language so I let you judge.

Reply: The manuscript got English editing service just before submission. We attached certificate from English editing service company.

Textcheck Certificate

Refnum:	22070720
Title:	Prediction of postoperative pulmonary complications in older patients undergoing lobectomy for lung cancer based on skeletal muscle mass
Date:	2022/07/19

We hereby certify that Textcheck has checked and corrected the English in the manuscript named above.

A specialist editor with suitable professional knowledge (M.Sc. or Ph.D./M.D.) reviewed and corrected the English. An English language specialist subsequently checked the paper again. The first language of both editors is English.

Please direct any questions regarding this certificate or the English in the certified paper to: certified@textcheck.com (Please quote our reference number: '22070720')

Second, the abstract does not mention major information as the number of patients included in the study.

Reply: For following the recommendation from Reviewer C and Reviewer B, we added the number of analyzed patients in Abstract.

Finally, after the few remarks on the form, here are my remarks on the substance of the article :

- I am surprised that the articles already published on the subject of the association between sarcopenia and morbidity after major surgery are not mentioned in the introduction.

Reply: We briefly described the association between sarcopenia and morbidity after major surgeries because we wanted to focus on the association between skeletal muscle mass, and “lung function” and PPCs after lung cancer surgery. However, we added it with relevant references as Reviewer C recommended. We also added as following in Introduction. “Previous studies have demonstrated that low skeletal muscle is associated with morbidity after major surgery [Silva de Paula N, et al. Sarcopenia and Skeletal Muscle Quality as Predictors of Postoperative Complication and Early Mortality in Gynecologic Cancer. Int J Gynecol Cancer 2018; 28: 412-20., Sun X, et al. Sarcopenia in Patients With Normal Body Mass Index Is an Independent Predictor for Postoperative Complication and Long-Term Survival in Gastric Cancer.

JOURNAL CITATION REPORTS IMPACT FACTOR 3.005 © 2022 Clarivate Analytics

Clin Transl Sci 2021; 14: 837-46., Trejo-Avila M, et al. Sarcopenia predicts worse postoperative outcomes and decreased survival rates in patients with colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2021; 36: 1077-96.]. Moreover, low skeletal muscle mass has been shown decreased lung function in the patients with lung diseases."

- There is no justification for the choice of muscle measured, which is not the most frequently used : in the literature, the psoas is often measured at L3 or L4, whereas here it is the EM at T12. It is conceivable that this measurement is more easily measured on thoracic scans performed as part of the preoperative work-up (whereas an abdominal scan is perhaps not systematically performed) but this deserves an explanation.
Reply: Psoas muscle has been popularly chosen as a predictor in previous studies for the association between muscle mass and morbidity after major surgeries. However, psoas muscle is originated from T12 and inserted to femur. Scanning from chest to lower limbs is required for the exact evaluation of psoas muscle and muscle mass at the mid-level of psoas muscle, taken from abdominal scanning, has been used in the previous studies. Therefore, we thought that psoas muscle was not appropriated. We added above in Discussion.

- In their introduction, the authors mention that sarcopenia is related to the decline in lung function, and that the decline in lung function is related to the occurrence of postoperative complications. Given that lung function tests are imperative in pre-operative thoracic surgery, I find it difficult to understand what the added value of measuring EM muscle on the pre-operative CT scan would be.
Reply: Preoperative PFT has been demonstrated as a reliable predictor for morbidity and mortality after lung cancer surgery in previous studies and clinically used. However, several conditions should be met to get the exact values of PFT. One of them is patient's understanding and effort at the exam. It means that PFT is an objective tool but contains subjective elements. Therefore, considering lung cancer surgeries have been performed in the elderly patients, we thought that more objective tool for the predictor is needed. We described above in Discussion.

- A flowchart with the number of patients excluded of the study, and the reason for exclusion would have been interesting. Indeed, it is noted that patients with pre-existing respiratory pathology are excluded. This implies that COPD patients, common in the pulmonary neoplasia cohort, were excluded.
Reply: Yes, we absolutely agreed Reviewer C's comment. Lung cancer had the common pathological mechanism with chronic obstructive pulmonary disease (COPD). We wanted to evaluate the exact association between preoperative PFT and skeletal muscle mass, and PPCs after lung cancer surgery. Therefore, we excluded the patients with COPD. We added above in Discussion.

- While in the literature, measurements of muscle area or mass are always indexed to height and sex, here this is not the case, even though the data is available. Why?
Reply: We did not adjust muscle mass intentionally with sex and body measurement.

As we described in Discussion, sarcopenia has been defined as CSA of the specific muscle indexed with body surfaced area less than median and its value was different according to sex. However, a consensus definition of sarcopenia has not been established. The European consensus statement recommendations are based on healthy young adults. Therefore, we evaluated just absolute value of CSA, not adjusted with sex and body measurement. However, the evaluation from larger population for association between sarcopenia defined by age, sex and individual activity and PPCs after lung cancer surgery might be helpful.

- The choice of the primary endpoint is debatable, the fact that it is composite allows the number of events to be increased, but it brings together elements of truly disparate severity. Moreover, each patient with PCP has only one diagnosis whereas it seems obvious that each patient can have several diagnoses.
Reply: Yes, we absolutely agreed Reviewer C's comment. The interactions among the events might be existed, although the events of PPCs were defined and listed. We described above as limitation in Discussion.

- The median CSA values in the two groups largely overlap, so although on average the muscle area is lower in patients who are going to have PPC, it does not seem possible to define a threshold distinguishing these two groups in this population.
Reply: Yes, we absolutely agreed Reviewer C's comment. We added Reviewer C's comment as limitation in Discussion as below. "The median of CSA_{Both} in the groups showed largely overlap and it seemed that the possibility of threshold to distinguish the two groups was low."

Reviewer D
Comments to Authors:
The research of sarcoenia is up-to-date and very important in modern clinical practice. The stratification of risk factors such a sarcopenia could be helpful in tailoring the antitumor therapy for individual patients.
The article depicts the relation between sarcopenia status and postoperative compliacions in patients suffering from lung cancer after resections.
For the evaluation of sarcopenia, the authors chose a morphological-quantitative method by evaluating CT scans at the 12th thoracic vertebra. The methodology of the article is clear and the results are statistically adequately managed. The valuable passage is the discussion itself. The number of citations testifies to a thorough study of the issue and the references are up-to-date.
I have few comments on the article:

Line 66: There must be depict the way of CT measurement of erector spinae muscles in more details - how was the region of muscle chosen - automatically or by single operator etc, specify the software...
Reply: We thank you for Reviewer D's comment. The region was chosen and measured manually, using software Centricity PACS Radiology RA1000 Workstation (GE Healthcare Inc., Chicago, IL, USA), by a radiologist who was blinded to the

study. We added above in Materials and Methods.
Sarcopenia is typical for older people. In the study the group with postoperative complications was significantly older. In the discussion there must be mentioned exactly what is the advntage in EM measurement against the simple information about the age of patients. The authors have only explained the advantage against the spirometry measurement.
Reply: We added as below in Discussion. "Therefore, measurement of skeletal muscle mass may be an alternative method, without requiring any special effort by the patient, to predict PPCs in older patients undergoing lobectomy for lung cancer, regardless of the surgical approach, VATS or thoracotomy. Considering the patients with PPCs were older than the patients without PPCs, measurement of skeletal muscle mass might be a useful and comfort tool for the elderly patients with lung cancer to predict PPCs after lung cancer surgery. Moreover, the evaluation for PPCs after lung cancer surgery was able to be simultaneously obtained at the first scanning for diagnosis of lung cancer, using CT. It meant that no additional assessment for PPCs after lung cancer surgery was needed.".

Reviewer E

Thank you for the opportunity to review this novel report entitled "Prediction of postoperative pulmonary complications in older patients undergoing lobectomy for lung cancer based on skeletal muscle mass".
This manuscript demonstrated the clinical impact of volume of the erector spinae muscle (EM) as a predictor of pulmonary complications (PPCs) in the retrospective study. The authors showed that the sum of cross-sectional areas of the EMs was a favorable predictor for the incidence of PPCs among lung cancer patients older than 65 as well as FVC and FEV1.
Unfortunately, I think this study does not reach enough quality to be accepted in Journal of Thoracic Disease. The present study includes many limitations; unclear definition of PCCs, insufficient calculation of EMs, and lack of several important factors concerning PPCs. Please refer the comments to improve the manuscript.
Reply: We thank Reviewer E's comments. We carefully read the comments and answered them.

Major comments
Introduction(L42-43)
I cannot understand the importance of EMs. There are major muscles for the evaluation of sarcopenia rather than EMs (e.g. psoas muscle (Baracos VE. Psoas as a sentinel muscle for sarcopenia: a flawed premise. J Cachexia Sarcopenia Muscle. 2017 Aug;8(4):527-528)). The authors should declare the reason to select EMs as skeletal muscle. In addition, it is important to compare the predictivity for the incidence of PPCs between EMs and psoas muscle.
Reply: We thank Reviewer E for the comment. As Reviewer E commented, previous studies have demonstrated the predictability of psoas muscle as morbidity. However, additional scanning was required for the evaluation of psoas muscle in the patients undergoing with lung cancer, because chest scanning for lung cancer did not cover

psoas muscle. It meant that psoas muscle as a predictor for morbidity in the patients with lung cancer was not suitable. Moreover, additional scanning increased the risk for the exposure of biohazard. We added above in Discussion, not Introduction.

Method(L69-72)
The measurement of EMs is the key for the credibility of the present research. However, the measurement is not reliable. I think EMs measurement should be done by several researchers and authors show the median and range of the measurement. In addition, the method for the calculation of cross-sectional areas of EMs is unclear. Please clarify the details of the measurement and software used.
Reply: We absolutely agree Reviewer E's comment. CSA of erector spinae muscle (EM) was measured manually by a radiologist who was blinded to the study. Therefore, we did not have any data for interobserver agreement. Although the previous studies for sarcopenia have also missed it [Nakada T, et al. Risk factors and cancer recurrence associated with postoperative complications after thoracoscopic lobectomy for clinical stage I non-small cell lung cancer. Thorac Cancer 2019; 10: 1945-52., Kawaguchi Y, et al. Sarcopenia predicts poor postoperative outcome in elderly patients with lung cancer. Gen Thorac Cardiovasc Surg 2019; 67: 949-54.], it was definite weak point for the present study. We added above as a limitation in Discussion. We described the measurement of CSA of EM in detail with description of the used software in Materials and Methods.

Method(L86-90)
I guess PPCs are the primary outcome of the study. The definition of PPCs is the most important for the significant of EMs. However, the definition is vague. Moreover, there is no reliable criteria for the PPCs. I think Clavien-Dindo classification is reliable criteria for the surgical complications. Please confirm the definition of PPCs. If possible, please refer the following paper (Lugg ST, Agostini PJ, Tikka T, et al. Long-term impact of developing a postoperative pulmonary complication after lung surgery. Thorax 2016; 71: 171-6).
Reply: Clear definition and confirmation of PPCs were critical in the present study, as Reviewer E pointed. Reviewer E recommended the use of "The Clavien-Dindo Classification" for clear definition and confirmation of PPCs in the present study. PPCs in the present study were defined as The Clavien-Dindo Classification. We added above description in Materials and Method. The study by Lugg ST et al. was cited as reference 1.

Results Table1
Table1 lacks essential clinical information of lung cancer. The authors should add the clinical or pathological stage, operation time, surgical information (the presence of bronchoplasty, angioplastic procedure, the resection of neighboring structures, and pleural adhesion when operation), and blood loss during operation. These are the factor related to the incidence of PPCs.
Reply: We added clinical information. However, some informations were missed. We described it as limitation in Discussion.

JOURNAL CITATION REPORTS IMPACT FACTOR 3.005 © 2022 Clarivate Analytics

Minor comments

1. Method L67-68

The protocol for the CT detection of EMs using CT scan within 1 week is very strict. Please indicate the median day before surgery to evidence the protocol is obeyed.

Reply: Preoperative PFT and chest computed tomography (CT) were performed within 3 (3-4) days and 3 (3-4) days, respectively.

2. Method

Please declare the details of the surgical procedure (skin incision, port location when VATS, thoracotomy procedure (posterolateral, anterior lateral, axillary, etc), and the preservation of muscle (latissimus dorsi muscle and serratus anterior muscle)). The surgical procedure may affect the incidence of postoperative complications.

Reply: We added surgical procedure.

3. Method L88-89

PPC is unclear. The authors should clarify the definition of persistent air leak (>5 day or >7 day?), pleural effusion, etc. I recommend to use Clavien-Dindo (>Grade3).

Reply: PPCs in the present study were defined as grade III in The Clavien-Dindo Classification. We added above description in Materials and Method.

4. Results Table 2

The authors show the data of FVC (L) and FEV1 (L). These are influenced by the height and weight. So, I think FVC (%) and FEV1 (%) are better.

Reply: We showed absolute values of preoperative PFT. We did not described them, adjusted by sex, age, height, weight and so on, following the guideline by European Respiratory Society and American Thoracic Society [Stanojevic S, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J 2022; 60: 2101499.], although institutional protocol used equation for Korean population by Choi et al [Tuberc Respir Dis 2005; 58: 230-42.]. The guideline showed that the inappropriate selection of equation for reference values leaded misinterpretation and serious problems. Moreover, various equations, not universal equation, has been introduced for Korean population. Therefore, we described absolute values of PFT, not absolute value/reference value (%). We added above in Discussion.

5. Discussion L172-174

I don't agree that "although PFT is an objective means of evaluating pulmonary, function, it is composed of subjective factors". PFT is not subjective but objective. Correctly, PFT is influenced by the patients' effort as the authors pointed out; therefore, the accuracy of PFT is not always assured.

Reply: We changed the sentence as following. "although PFT is an objective means of evaluating pulmonary function, it has the possibility misinterpretation."

6. Discussion L174-175

I think EMs is equal to PFT in terms of predictivity of PFT for PPCs. Certainly, PFT required the patients' effort, on the other hand, EMs evaluation brings radiation exposure. Therefore, PFT is not inferior to calculated EMs. So, I think the sentence is

JOURNAL CITATION REPORTS IMPACT FACTOR 3.005 © 2022 Clarivate Analytics

unreasonable.

Reply: We change the description, “more objective” into “an alternative”. Although measurement of skeletal muscle mass has the exposure of radiation, the exposure is not additional. With the scanning for diagnosis of lung cancer, the measurement of skeletal muscle mass is simultaneously performed and additional exposure of radiation is not taken.