Author's response to reviews

Title: the effects of pulmonary rehabilitation versus chest physical therapy on the levels of fibrinogen and albumin in patients with lung cancer undergoing lung resection: a randomized clinical trial

Authors:

Maria Tereza A P Morano (ttmorano@hotmail.com)
Rafael Mesquita (rafaelmesquita14@ymail.com)
Guilherme P F da Silva (guilhermepinheiro87@hotmail.com)
Amanda S Araujo (amandafisio@hotmail.com)
Juliana Maria S Pinto (jumsp@hotmail.com)
Antero G Neto (anterogn@terra.com.br)
Cyntia Maria S Viana (cynthiav561@gmail.com)
Manoel O de Morais Filho (odorico@ufc.br)
Eanes D B Pereira (eanes@fortalnet.com.br)

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Author's response to reviews: see over
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Title: the effects of pulmonary rehabilitation versus chest physical therapy on the levels of fibrinogen and albumin in patients with lung cancer undergoing lung resection: a randomized clinical trial

Reviewer Paolo Solidoro

We would like to thank the reviewer for these important comments

Major Compulsory Revisions
1. Is the question posed by the authors well defined?
I don’t think so. Reading the paper it seems that rehabilitation has a role in reducing inflammation in lung cancer. Probably it’s more correct to say that we have a reduction of inflammation in inflammatory comorbidities (interstitial lung diseases, obstructive lung diseases, infectious diseases) of patients with lung cancer
Response: All our 24 lung cancer patients presented previous pulmonary disease, most of them with chronic obstructive pulmonary disease (COPD). We agree that rehabilitation has a role in reducing inflammation in inflammatory respiratory comorbidities of patients with lung cancer (discussion section)(line 209-212,242-246)

2. Are the methods appropriate and well described?
We have two groups with lung diseases and cancer, before and after two different kinds of rehabilitation; we have no idea about other therapies (corticosteroids?, Bronchodilators?) of these etherogeneous groups. Probably other therapies can influence the reduction of fibrinogen more then rehabilitation. Moreover if you want to understand the effects of rehabilitation on lung cancer you need a group with lung cancer without other pulmonary comorbidities and therapies.
Response: We agree that the presence of respiratory comorbidities and other therapies (corticosteroids?, Bronchodilators?) can influence the reduction of fibrinogen. However, after randomization, the two groups(pulmonary rehabilitation and chest physical therapy) were well-balanced regarding the presence of previous pulmonary disease and others baseline characteristics (table 1). Eighty percent of the respiratory comorbidities was COPD and the two groups did not differ according to the severity of COPD, for the GOLD stage III 50% of the patients were in the pulmonary rehabilitation group(PR) and 60% were in the chest physical therapy(CPT).(result section, line 173-177)(discussion section line 261-267) . We tried to balance the groups for the presence and severity of previous inflammatory pulmonary disease so they did not differ systematically at the outset of the experiment.
3. Are the data sound?
It’s impossible to understand the role of rehabilitation in lung cancer if we don’t know other therapies

Response: We agree that knowing other therapies is important. But we tried to balance the groups for the presence and severity of previous pulmonary disease so they do not differ systematically at the outset of the experiment and any difference that subsequently arises between them can be attributed to the program. (discussion section line 261-267)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Data are interesting but difficult to analyze
Response: we improved the reporting of data (result section)

5. Are the discussion and conclusions well balanced and adequately supported by the data?
There is a great bias in selecting patients
Response: we agree there is a bias selecting patients with lung cancer and chronic inflammatory pulmonary disease. This is reported in discussion section line 242-246, 261-267).

6. Are limitations of the work clearly stated?
No. The limitations referred have to be a least described in the article
Response: we agree and limitations was described in the article (discussion section line 257-267)

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
1) The prognosis of patients undergoing surgery probably is related to fibrinogen too, but fibrinogen increases because of either lung cancer or comorbidities and 2) comorbidities are pivotal in prognosis and survival after lung surgery.
Response: We are not sure if we fully understand this comment, but we believe this reviewer wanted to suggest that comorbidities could have compromised our results. We do agree that comorbidities can have an influence on the levels of fibrinogen, but we do not think they have compromised our results. In our study patients were randomized to each group and this led to a similar distribution of comorbidities between the two groups. Therefore, if there was any influence of comorbidities, this influence would have occurred in both groups, not necessarily compromising our analyses. Nevertheless, we opted for adding some text to the manuscript in order to discuss these aspects (see in the Discussion section 242-246).

8. Do the title and abstract accurately convey what has been found?
I don’t think so, it has to be reviewed following the correction of the described bias (comorbidities, therapies). Probably in the title should be more correct writing “in patients with inflammatory lung diseases and cancer undergoing lung resection”
Response: change accepted title and abstract
We would like to thank the reviewer for these important comments

Minor Essential Revisions
The study is interesting, because it takes into account an easily measurable marker of inflammation, and enhances the importance of preoperative pulmonary rehabilitation in reducing postoperative complications.

Only minor comments:
1. What does it mean normal lung function? It would be appropriate to specify which parameters have been considered and their cut-off of normality.
   **Response:** For normal lung function we considered following spirometric parameters: FEV₁/ FVC above 0.70 and FVC, FEV₁ above 80% of the predict value. (methods, line 119).
2. There are no reports of the arterial blood gas analysis data
   **Response:** the arterial blood gas analysis data were included (table 1).
3. Missing the effects of rehabilitation on the 6MWD.
   **Response:** the effects of rehabilitation on the 6MWD is described in the article (table 2) Results section line 199-201.

We would like to thank the reviewer for these important comments

Major Essential Comments:
The article is in general well written, and the conclusions likely supported by the data. As a rule, it is best to present data in the same format within variable – the bar/SD and whisker-box presentation in figure 2 is not good. The statistics should be two-way ANOVA with repeated measures, not individual group t-tests or comparison of deltas within group with unpaired t-tests. An appropriate post hoc test will answer the questions.

**Response:** One of the major comments by this reviewer was that a two-way ANOVA with repeated measures should replace individual group t-tests or comparisons of deltas within-group with unpaired t-tests. According to Portney and Watkins (Foundations of clinical research: applications to practice. 3rd ed. Upper Saddle River: Prentice Hall; 2008), a two-way ANOVA with repeated measures should be used when there are two within-subjects factors, and in our study we have one within-subject factor (time) and one between-subjects factor (group). Therefore, a mixed between-within subjects ANOVA is more appropriate. This test was performed and the results were added to the manuscript, replacing previous results (see Results line 178-205). Of note, the interpretation of the results did not change, i.e., compared to chest physical therapy, pulmonary rehabilitation can reduce serum fibrinogen levels in patients with lung cancer who were eligible for lung resection. Some changes were also necessary in the Statistical analysis subsection (see Methods line 151-160).
Minor Comments:

Response: this reference is important and it is commented in our article. (discussion section, line 234)