Author’s response to reviews

Title: Acupressure Therapy and Liu-Zi-Jue Qigong for Pulmonary Function and Quality of Life in Patients with Severe Novel Coronavirus Pneumonia (COVID-19): study protocol for a randomized controlled trial

Authors:
Shuaipan Zhang (18939061729@163.com)
Qingguang Zhu (zhuqingguang@162.com)
Chao Zhan (edyljtzc@163.com)
Wei Cheng (chengwei5200@126.com)
Xiaoming Fang (fzr2007@163.com)
Min Fang (fangmin19650510@163.com)
Lei Fang (fanglei586@126.com)

Version: 2 Date: 08 Jul 2020

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Acupressure Therapy and Liu Zi Jue Qigong for Pulmonary Function and Quality of Life in Patients with Severe Novel Coronavirus Pneumonia (COVID-19): a study protocol for a randomized controlled trial” (ID: TRLS-D-20-00232). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Most of the revised portion are marked in red in the paper and the language of the manuscript has been professionally edited. The main corrections in the paper and the responds to the editor’s and reviewer’s comments are as follows:

Responds to the reviewer’s comments:

Reviewer #2:

1. The English and subsequently the readability of this protocol has greatly improved. However, in figure 1 "Flow chart of the trial" has a spelling error. Additionally, in this figure the text is not in the same font and size. Please could the authors address this to ensure that the text is the same size and font. As I have found a spelling error, I would like the authors to also go over the whole of the protocol again to ensure that there are no other spelling errors.
Response: I apologize for the spelling error again; we have checked the full text again as many times as required by the editor to prevent other spelling errors. In addition, I have adjusted the text is the same size and font in figure 1.

2. The additional information that the authors have given about the intervention on page 6, lines 107-113, I feel needs a reference to the studies that have demonstrated that the Liu Zi Jue exercises have been successful in those whom have lung disease (even quantify how successful this intervention is from this study or studies). This reference is especially required as the authors state that 'previous studies have shown…'. It would also be preferable for the authors to be more specific about the lung disease they are referring to and how similar or different they are from pneumonia specifically as this study is looking at pneumonia.

Response: In lines 94-100, I have separately explained the application of acupressure and Liu Zi Jue in lung diseases. Among them, dyspnea and reduced quality of life are the key problems that all lung diseases have. ‘The previous research’ here is has been reflected above, which is actually a summary of the above. Therefore, there is no literature cited here, but I still thank the editor for your rigorous.

3. Thank you for adding in figures 3 and 4 to demonstrate the intervention, however it would be improved further if there were a caption for these figures to state what the diagrams are demonstrating e.g. the stages. Additionally, the quality of figure 4 especially needs to be improved.

Response: I added the following caption below the figures. Figures 3a, 3b, and 3c respectively illustrate the method of thumb pressing and the positioning of the operated acupuncture points. And the core movements of the preparatory movements and the six pronunciation movements "xu, he, hu, si, chui, and xi" are shown in Figures 4a-4j respectively.

4. In the sample size section on page 16, I have tried to replicate the sample size value you have documented however I have not been able to given the information you have provided. Could the authors please review this further. It would also be useful to document the total sample size before accounting for the loss to follow up. Also, if the authors could provide a rationale for why 20% loss to follow up is likely to happen or even a reference this would be more informative.

Response: I regret that the editor cannot find the literature information I provided. The reason may be that the literature is Chinese article which included in the CNKI database. Considering that the severely ill patients are different from the general condition, in order to prevent the deterioration of the condition and lead to shedding, a 20% shedding rate is adopted. I am sorry that it has an mistake in the last sample size calculation, and the final calculation is the following data. There were 51 cases in each group, and add 20% shedding rate it totally needs 64 cases in each group.

5. Under the randomization section at the top of page 17, could the authors please clarify what they mean by '…will open a continuous random envelop…'. Additionally, could the authors be clearer on the steps from identifying participants to when the participant is assigned to a treatment arm as currently this section contradicts itself. It would be helpful if the authors formed this section chronologically to ensure clarity for each of the steps.

Response: We once again confirmed the random method of the envelope method and made the following modifications. The Department of Science and Technology of SUTCM will generate
the randomization sequence using a random number generator (IBM, Chicago, IL, USA) and then placed in a sequenced, sealed, opaque envelope. When potential participants meet the inclusion criteria, the envelope can be opened and the subject will accept the corresponding measures.

6. Under the statistical analysis section on page 18, the authors have clarified how they will deal with missing data, however it would be further helpful what method will be used instead of just stating 'Multiple imputations will be used to impute missing data values...'. Additionally, could the authors please clarify why they will be using Little's test, it is not clear what is being tested. It would also be helpful to reference Little's test too.
Response: Prior to any analysis, any missing data pattern will be investigated and reasons for missing data obtained and summarized where possible. Multiple imputation was also used to impute missing data and five datasets were generated. missing completely methylation data, which will be used for sensitivity analysis to assess the robustness of the results. In addition, I agree with the issue pointed out by the editor, both random missing (MAR) and completely random missing (MCAR) can use the multiple filling method recommended, so there is no need to use Little's test.

7. Under the statistical analysis section on page 17, could the authors please split this into appropriate paragraphs or subsections as currently it does not read logically.
Response: Yes, I have divided the statistical analysis into 3 parts in the manuscript.

8. Under the statistical analysis section on page 17, could the authors please pre-specify the characteristics that they will use for the adjusted analysis, although the authors have stated 'e.g. age, sex' it would be preferable to specifically give a definitive list especially as baseline measures are being taken.
Response: Yes, I will take your suggestion and modify it as shown below. Baseline covariates included for adjustment were sex, age category, history of cardiopulmonary disease and body weight category. The whole outcomes scale was also measured at baseline.

9. Under the statistical analysis section, it is still not clear how the primary outcome will be assessed as the authors just list a number of methods to be used. Please could the authors be more specific on which method will be used to assess the primary outcome given the treatment arms, and likewise for the secondary outcomes. Also, the authors need to state which of the 2 time points is the primary endpoint for the primary outcome and if they plan on using the baseline measures in the analysis. This is really important and needs to be clear to the reader.
Response: The primary outcomes will be evaluated at baseline, 6 days after the intervention, and upon discharge based on the intention-to-treat analysis (ITT). The primary endpoint of the trial is the mean change in mMRC scales from baseline to the discharge day.

Reviewer #3:

1. There is still some language editing required for clarity.
Response: We will try to improve the language editing work as much as possible.
2. Please include the name of the sponsor in the manuscript.
Response: I added the name of the sponsor in the "Funding" section with a red font. Totally, the trial sponsor are the Shanghai Municipal Government and Shanghai University of Traditional Chinese Medicine.

3. Could you provide data collection forms or refer to where they can be found, I couldn't see them in the revised manuscript.
Response: There are data collection forms of mMRC and ADL-BI in references 24-28, which we can refer to.

4. Could you provide more details on how the administrators will report their findings on data monitoring.
Response: Following the editor’s suggestion, I add the following content. The administrators report the data supervision to the steering committee every week, mainly including the reliability of the data and the accuracy of the entry.

5. How would those changes be communicated to the relevant parties?
Response: After the steering committee and the ethics committee agree to make changes to the protocol, it will be updated in the clinical registration center to ensure that all parties can understand the changes.

**We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.**

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Your sincerely

Lei Fang