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

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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 editor’s comments:

1. Primary outcome needs to be very explicit. What assessment time?
Response: We will use mMRC as the primary outcome indicators to evaluate the dyspnea symptoms and physical health. Evaluating outcomes will at three points (before treatment, 7th day during hospitalization and the discharge day).
2. English language needs to be improved.
   Response: We have sought the native English speakers to revise the full text for better understanding by editors and reviewers. The editing certificate has been unloaded as additional file 4.

3. The long list of protocol variations needs to be removed. Patients should be free to withdraw from the trial at any time, but other than this there should be no exclusions.
   Response: The long list of protocol variations had been removed. During the intervention period, patients have the right to withdraw whatever the reason and time under the protection of Declaration of Helsinki.

4. It is unclear why envelopes are needed if the randomization is by phone.
   Response: The phone is not necessary and when potential participants meet the inclusion criteria, the study coordinator will open a continuous random envelope and inform the subjects of their group assignment.

5. Randomization should be performed after the eligibility assessment and after baseline assessment.
   Response: Your suggestion is very useful; I have added the description of this sentence in the "randomization" section.

6. Clarify if the outcome assessor is blind (is this the patient?)
   Response: The outcome assessors are independent while the patients are the targets of outcome evaluation. To reduce the risk of bias, outcome assessor, data managers, and statisticians were unaware of group assignments during the outcome evaluation and data analysis process.

7. No baseline testing is appropriate in an RCT
   Response: Ok, I read the relevant literature and decided not to overemphasize the testing baseline difference. I have deleted the relevant description in the "Statistical analysis" section.

8. No within group testing is appropriate here. If there are baseline measures of the outcome then the appropriate analysis is an ANCOVA type approach adjusting for the baseline value.
   Response: Yes, the main focus of this manuscript is the difference between the intervention group and the control group. Baseline evaluation does not need to pay too much attention according to the opinions of reviewers, and can be secondly analyzed with logistic regression models.

9. The primary analysis should be ITT. Secondary analysis of per protocol will not preserve the random allocation and so if interest is in efficacy (as opposed to effectiveness) then consider a CACE analysis.
   Response: Multivariable logistic regression models have been developed to adjust for clinical characteristics (e.g., age, sex) estimated the intervention efficacy.

10. Please clarify if the primary analysis will be conditional on the time points of measurement or averaged over all measurement occasions.
Response: We clarify that the primary analysis will be conditional on the time points of measurement.

11. Please provide a translated copy of the informed consent information.
Response: We have uploaded the additional file 2 as the English version of the informed consent.

12. Patients should be allowed to participate in normal exercise under the intervention condition.
Response: Yes, I have added this suggestion in the intervention section. Both groups of the participants will be allowed to participate in normal exercise under the intervention conditions.

Responds to the reviewer’s comments:

Reviewer #1:

General

1. I feel it is not made clear that this is a pilot study. Please see this guide to reporting https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-019-0423-8
Response: I have browsed the reporting guide of the pilot study according to your suggestion and the structure and content of the article have been modified in many places.

Abstract

2. Is aged 20 to 80 inclusion criteria or are you describing the participants?
Response: Patients are aged between 20 and 80.

3. Three clinical assessment points are given. What happens if discharge is \( \leq 7 \) days?
Response: The data showed that the average length of hospitalization of critically ill patients was about 9 days, and that in Hubei province was about 20 days. If the hospitalization time was less than 7 days, the subject will be excluded as the outcome evaluation cannot be completed.

4. Check for use of trial instead of trial.
Response: I am so sorry for the spelling error and I have modified it in the whole manuscript.

Methods/design

5. Please be clear about allocation concealment. This seems to be implied by random envelopes but contradicted in other places in the text.
Response: The allocation concealment is implemented with an opaque envelope; the specific process is described below. Randomization should be performed after the eligibility assessment and after baseline assessment. Department of Science and Technology of SUTCM will generate the randomization sequence using a random number generator (IBM, Chicago, IL, USA) and then sequentially number them in an opaque envelope. When potential participants meet the
inclusion criteria, the study coordinator will open a continuous random envelope and inform the subjects of their group assignment.

6. The paper states 'As long as any of the following conditions are met, it will withdraw' and five situations are explained. Does this refer to withdrawal of treatment or withdrawal from the study? If this is withdrawal from the study please consider if this would introduce bias. Response: It will cause bias if they are doped out of the study, so I have modified the withdrew condition in the manuscript which is as follows: During the intervention period, patients have the right to withdraw whatever the reason and time under the protection of Declaration of Helsinki. In addition, if the hospitalization time was less than 7 days, the subject will be excluded as the outcome evaluation cannot be completed.

7. The sample size calculation does not provide information on the minimally clinical important difference. The calculation lacks information to allow replication. No allowance has been made for multiple outcomes. Response: PASS software (PASS 11. NCSS, LLC. Kaysville, Utah, USA) will be used to estimate the sample size utilizing two independent sample means ($\alpha = 0.05$, $\beta = 0.10$). We will use the mMRC as the primary efficacy outcome. Based on previous clinical studies on the effect of respiratory symptoms after acupressure therapy plus Liu Zi Jue Qigong interventions, the mMRC scale score in the control group is 0.52 with a standard deviation of 0.11, and the average mMRC scale score in the treatment group is 0.95 with a standard deviation of 0.92. In this study, the target sample size will be 72 participants, anticipating on maximum loss to follow up of 20%.

Statistical analysis

8. The statistical analysis plan does not give sufficient detail of the analysis of the primary outcome(s). It is not clear what analysis is planned here. Response: Statistical analysis will be performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Multiple imputations will be used to impute missing data values if there is more than 5% missing data and Little’s test is statistically significant. The primary and secondary outcomes will be evaluated at baseline, 6 days after the intervention, and upon discharge based on the intention-to-treat analysis (ITT). These clinical scales will be converted into continuous variable data. A Kolmogorov-Smirnov test with Lilliefors correction will be used to analyze all quantitative variables to determine whether they follow a normal distribution. Nonnormally distributed data will be expressed as the median (upper and lower quartiles), and normally distributed data will be expressed as the mean ± the standard deviation (SD). Categorical variables will be presented as frequencies and percentages. When the data have a normal distribution, two-way repeated-measures ANOVA will be used as the main analytic method, and a paired sample t-test will be used between the two intervention groups; if the normal distribution is not met, the Wilcoxon test will be used as an alternative method. Multivariable logistic regression models will be developed to adjust for clinical characteristics (e.g., age, sex) to estimate the intervention efficacy. The level of significance will be $\alpha < 0.05$ with a two-tailed test. Adverse events will be listed and analyzed using the chi-square test or Fisher’s exact test.
9. The plan of analysis suggests differences in the characteristics of those allocated to intervention and control groups will be tested at baseline. This is not appropriate. Please see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3286439/
Response: I had read the link you gave and deleted the content of the comparison within the group in the statistical analysis, they are really meaningless.

10. It is unclear what kind of data type the primary outcome(s) will be and how this will be allowed for in the analysis.
Response: The primary outcome as a clinical scale will be converted into continuous variable data and be compared between groups.

Reviewer #2:

1. * I found the protocol paper difficult to read due to the spelling mistakes and also the language that was used. Many sentences did not make sense and also were not formed correctly. There were too many incidences of this occurrence and so I cannot mention them all. Therefore, I would advise that the authors would benefit from someone whom English is their first language to read over this manuscript to greatly improve the readability.
Response: We are so sorry for the spelling mistakes and language issue. We have asked the English-speaking staff to edit the manuscript language as required to make it easier for reviewers to understand the content of the article.

2. * On page 3, line 49-50, the authors state that only one rapid advice guideline has been used, I find this hard to believe so I think this needs to be time stamped to highlight the time of when the research into the background was completed whereby this was correct. Especially as this area is rapidly evolving and updates are being made to such guidelines.
Response: I may not have made it clear. The rapid advice guideline I refer to is the National Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia (The 7th Trial Version), which was promulgated by National Health Commission of the People’s Republic of China. It is indeed constantly updated with the rapid development of COVID-19, and ultimately it is the 7th Trial Version.

3. * As part of the background and discussion sections the authors make reference to how the intervention has been used previously. However, this is not clear enough, this needs to be expanded on greatly to persuade the reader that using this intervention could be applied to the proposed type of patients in the study the authors are wanting to complete. I think that the authors need to address such things as: How relatable is the previous research on this intervention to this study, also the similarities/differences in these types of patients that would indicate that there is sufficient logic to assess if such an intervention could be appropriate. It also occurred to me what the current practice is for those with pneumonia and if indeed this is something that had been thought about.
Response: Yes, I added the following to strengthen the logical relationship between the application of intervention methods in patients with COVID-19. Regarding COVID-19 patients, dyspnea is the most obvious clinical symptom. Furthermore, sudden illness and fear of disease are psychological disorders that each patient will have. Previous studies have shown that
Acupressure and Liu Zi Jue exercises can improve the respiratory symptoms of patients with lung disease as well as improve their quality of life and mental health. Therefore, effectively combining the two interventions into a rehabilitation method can potentially be used in the clinical rehabilitation of COVID-19 patients.

4. * The protocol for this study could be greatly improved if there was a diagram of what the intervention was and how it would be implemented, i.e. an instruction diagram. This can give the reader a greater understanding of what the intervention is.
Response: Your suggestion is very useful; The acupuncture points and Liu Zi Jue exercises are shown in figure 3 and figure 4 respectively in the manuscript.

5. * Under the section "Drop out and suspension criteria" the authors state in point (5) 'Researchers do not consider the participants appropriate to continue participating in this research'. This is not an adequate form of stopping criteria for a patient in such a trial, there needs to be specific criteria in which a patient would need to meet, not on the decision of the researchers, this could lead to bias being induced into the study.
Response: Yes, patients shedding should be determined by the subjects themselves, not by the researchers to prevent bias. During the intervention period, patients have the right to withdraw whatever the reason and time under the protection of Declaration of Helsinki21. In addition, if the hospitalization time was less than 7 days, the subject will be excluded as the outcome evaluation cannot be completed.

6. * Some of the subheadings under primary and secondary outcome measures are acronyms please can these be written out in full.
Response: The subheadings under primary and secondary outcome measures has been written out in full.

7. * Under the sample size calculations section, the author's state that the primary outcome is MDS. However, this is not reflected in the rest of the protocol. The authors state that there are two primary outcomes in the rest of the protocol. The authors either need to choose which one is there primary outcome and move the other to the secondary outcomes or state that the two primary outcomes as currently documented are co-primary outcomes and this needs to be reflected in the sample size calculations.
Response: I have selected Modified British medical research council (mMRC) as the only primary outcome. At the same time, I also cited the corresponding literature in the sample size calculation section, with mMRC as the primary efficacy outcome.

8. * Additionally, in the sample size calculations section, there is not enough information to replicate the calculation and arrive at a sample size of 120 participants. Please could the authors provide further clarification on the information that they used and how they arrived at a sample size of 120 participants.
Response: PASS software (PASS 11. NCSS, LLC. Kaysville, Utah, USA) was used to estimate the sample size by means of two independent sample means, \((\alpha = 0.05, \beta = 0.10)\). We take the mMRC as the primary efficacy outcome. Based on previous clinical studies on the effect of respiratory symptoms after Acupressure therapy plus Liu-zi-jue Qigong intervention, the mMRC scale score in the control group is 0.52 with a standard deviation of 0.11, and the average mMRC
scale score in the treatment group is 0.95 with a standard deviation of 0.92. In this study, the target sample size will be 72 participants and anticipating on maximum loss to follow up of 20%.

9. * Under the randomization section, I wondered if the authors had thought about a more sophisticated way of completing the randomization apart from using a simple random number generator. For example, minimization, block randomization etc. Additionally, in this section, the phrasing of how the participants will be allocated to each arm gets quite confusing, this needs to be looked at further and ensure that it is clear to the reader how the allocation of treatments to the participant is completed.
Response: I modified the randomized section of the manuscript to make it clearer with the random number generator method, third-party researchers opened the sealed envelopes in order to prove the allocation concealment, and finally randomly assigned the participants to the two groups. Randomization should be performed after the eligibility assessment and after baseline assessment. Department of Science and Technology of SUTCM will generate the randomization sequence using a random number generator (IBM, Chicago, IL, USA) and then sequentially number them in an opaque envelope. When potential participants meet the inclusion criteria, the study coordinator will open a continuous random envelope and inform the subjects of their group assignment. Then eligible patients will be randomly divided into a guideline therapy group and a guideline therapy plus TCMR group, with an allocation proportion of 1:1.

10. * Under the section 'Blinding', it does not state if those that are recruiting the participants know of the treatment and the objectives of the study. This needs to be detailed, as if those recruiting the participants know of the interventions and objectives of the study, they may be able to induce bias in terms of if such a patient should be included into the study.
Response: Due to the specific physiotherapy intervention, the participants are unable to be blind about group assignments, they will know the interventions and objectives of the study as a research limitation. However, what we can do is that the outcome assessor, data managers, and statisticians were unaware of group assignments during the outcome evaluation and data analysis process.

11. * Under the 'Data collecting and monitoring' section, the authors state that they will 'exclude the data if very few data are lost'. I am unsure as to what this means and therefore needs to be made clearer. I would like to know if the authors had considered using multiple imputation to impute on the missing data values. Currently the statistical analysis is inferred that complete case analysis would be completed however this needs to be explicitly stated.
Response: I declare that the " exclude the data if very few data are lost " I wrote is inappropriate, so I have deleted the sentence. For the processing of missing data, multiple imputation to impute on the missing data values should be adopted according to your suggestion. I added relevant content in the statistical analysis section of the manuscript.

12. * Under ' Statistical analysis' section, the authors state that mean and standard deviations will be used (line 334), however the authors should also state that the median and interquartile range will be reported if the continuous variable is not normally distributed i.e. skewed.
Response: In this section, I have added the consideration of whether it is normally distributed and the following content: “Nonnormally distributed data will be expressed as the median (upper
and lower quartiles), and normally distributed data will be expressed as the mean ± the standard deviation (SD). (345-347).”

13. * Additionally, in the statistical analysis section, for the demographic baseline information the authors will test to see if there is a difference between the groups, however, as this is an RCT then the randomization should be sufficient enough to ensure that the baseline characteristics are balanced. Current literature is of the opinion that testing between groups for baseline characteristics in an RCT is not required due to the nature of the study. If by looking across the groups for each of the baseline characteristics and there seems to be imbalance then this is due to the randomization. This would then imply adjustment in the main statistical analysis. However imbalanced across the two treatments should not be tested.
Response: Your suggestion updated my understanding of the baseline data processing method in the randomized controlled trial, so I have deleted my comparison of baseline content between groups.

14. * Again, within this section it is unclear as to how the analysis for each of the primary and secondary outcomes will be performed. Additionally, it would be advised to pick one of the follow up times to be the main primary outcome assessment and the other to be assessed as a secondary outcome. Therefore, a linear regression model could be used to assess the outcome whilst adjusting for the baseline measurement. As it stands the statistical analysis section needs to be made clearer to the reader on what exactly is going to be assessed and how with relation to the primary and secondary outcome.
Response: Statistical analysis will be performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Multiple imputations will be used to impute missing data values if there is more than 5% missing data and Little’s test is statistically significant. The primary and secondary outcomes will be evaluated at baseline, 6 days after the intervention, and upon discharge based on the intention-to-treat analysis (ITT). These clinical scales will be converted into continuous variable data. A Kolmogorov-Smirnov test with Lilliefors correction will be used to analyze all quantitative variables to determine whether they follow a normal distribution. Nonnormally distributed data will be expressed as the median (upper and lower quartiles), and normally distributed data will be expressed as the mean ± the standard deviation (SD). Categorical variables will be presented as frequencies and percentages. When the data have a normal distribution, two-way repeated-measures ANOVA will be used as the main analytic method, and a paired sample t-test will be used between the two intervention groups; if the normal distribution is not met, the Wilcoxon test will be used as an alternative method. Multivariable logistic regression models will be developed to adjust for clinical characteristics (e.g., age, sex) to estimate the intervention efficacy. The level of significance will be α < 0.05 with a two-tailed test. Adverse events will be listed and analyzed using the chi-square test or Fisher’s exact test.

Reviewer #3:

1. This is a timely trial as it is important to find adjunctive treatments for this condition. There are a number of specific comments about the trial protocol that need addressing which are listed below. More generally, the manuscript needs extensive revision by an English speaker for
language. In most places where there are errors, the meaning is clear, but the grammar or spelling is incorrect. In some places however, the errors make the meaning unclear.
Response: Yes, we have asked native English-speaking editors to make language changes to the manuscript.

2. 2b It is recommended to include a table of WHO organization Trial Registration Data Set in the manuscript.
Response: We have added an Additional file 3 as the table of WHO organization Trial Registration Data Set in the manuscript. However, I don’t quite understand the content, so I look forward to the reviewers to give corresponding comments.

3. 5b Please specify the name and contact information for the trial sponsor.
Response: For COVID-19, the trial sponsor are the Shanghai Municipal Government and Shanghai University of Traditional Chinese Medicine. The final fund management is performed by the Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated to Shanghai University of Traditional Chinese Medicine. The public contact email is yykyc2004@163.com.

4. 5c Please specify the role of the sponsor if applicable
Response: The funders had no role in the design of the study, analysis, collection, and interpretation of the data, or the writing and decision for publication of the manuscript. All these funding is a wider group of projects and apply to this study.

5. 6b Please explain the choice of comparator - why did you choose standard therapy?
Response: For the emergency event of COVID-19, standard therapy is a standard therapy developed in strict accordance with the National Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia (The 7th Trial Version). For patients, standard therapy is necessary to prevent death and other adverse consequences.

6. 7 Could you clarify what you mean by your second research question on page 6.
Response: I have modified the research question and turned it into a hypothesis. We make a hypothesis that official conventional therapy plus TCMR has better clinical efficacy than single conventional therapy on clinical symptoms, mental health and quality of life.

7. 8 Please confirm this is a superiority trial.
Response: This is a single-center, parallel-arms, superiority randomized controlled trial (RCT).

8. 11c Please describe strategy for monitoring adherence to the intervention, especially the Liu-zi-jue Qigong
Response: The nurse informs the patient to perform Liu-zi-jue exercise every day at 9 am and 4 pm. Each ward of the subject has remote monitoring so that the remote monitoring of the training of the subject can be achieved, and the participants are required to sign in as a diary after each exercise. Eventually, participants who can complete the training will be rewarded with monetary rewards.
9. Could you clarify the clinical assumptions in arriving at your sample size? What level of improvement were you looking for to get this result?
Response: PASS software (PASS 11. NCSS, LLC. Kaysville, Utah, USA) will be used to estimate the sample size utilizing two independent sample means ($\alpha = 0.05$, $\beta = 0.10$). We will use the mMRC as the primary efficacy outcome. Based on previous clinical studies on the effect of respiratory symptoms after acupressure therapy plus Liu Zi Jue Qigong interventions, the mMRC scale score in the control group is 0.52 with a standard deviation of 0.11, and the average mMRC scale score in the treatment group is 0.95 with a standard deviation of 0.92. In this study, the target sample size will be 72 participants, anticipating on maximum loss to follow up of 20%.

10. Please clarify who will enroll participants.
Response: The informed consent process was conducted by the principal investigator (LF) or study coordinator (WC) which will screen participants to confirm that potential participants meet the eligibility criteria listed below if the participants agree to sign the informed consent.

11. If possible, please provide data on the reliability and validity of the MDS and ADL primary outcome measures. Please provide data collection forms or refer to where they can be found.
Response: Modified Medical Research Council (mMRC) dyspnea scale and Activities of Daily Living Barthel Index (ADL-BI) Scale were used as the primary and secondary outcome measurements. They were widely used to evaluate the dyspnea symptoms and activities of daily living, which has been proved with good reliability and validity in the trials.

12. Please detail any plans to promote participant retention.
Response: An adequate retention plan is a valuable component of the research design process that can enhance participants’ ties with the researchers and the study. First, we will establish a local retention working group including the research coordinator and nurses. The coordinator and nurse will be fully trained before the trial starts; by focusing on daily communication strategies, they can improve retention after receiving additional attention. Furthermore, it is useful to provide sufficient funds within the study budget to compensate the nurses and participants for retention. Subjects will be monitored from a distance while completing their daily physical therapy with a diary recording.

13. Please list any measures to promote data security and how it will be stored.
Response: The administrators in Science and Technology Department of SUTCM will be responsible for monitoring the data management. The test data is recorded on the sub website of China Clinical Trial Center (http://www.medresman.org.cn/login.aspx) electronic data management system. Paper CRFs will be designed to collect test data according to the trial protocol, which will be stored in a securely locked location. We will conduct a double independent data entry to promote the data quality, then locked and analyzed it by an independent statistician under the supervision of the principle investigator. Electronic database will be closed after data entry is completed.

14. Please explicitly describe which participants will be included in the main analyses and define the study group in which they will be analyzed (e.g. as randomized).
Response: All main analyses will be carried out at the three-time points assessments between two groups and will be based on the intention-to-treat principle.

15. 21a Please declare the data administrator in the Science and Technology Department is independent and how they will report.
Response: The administrators at the Science and Technology Department of SUTCM will be responsible for monitoring data management as an independent third party. Paper Case Report Forms (CRFs) will be designed to collect test data according to the trial protocol, which will be stored in a securely locked location. We will conduct double independent data entry to promote data quality. Then, it will be locked and analyzed by an independent statistician under the supervision of the administrators. The test data will be recorded on the sub website of China Clinical Trial Center (http://www.medresman.org.cn/login.aspx) electronic data management system. The electronic database will be closed after data entry is completed.

16. 21b Please describe any interim analyses planned.
Response: Interim analysis will not be conducted.

17. 25 Please give more detail on plans to communicate important protocol modifications to relevant parties.
Response: If necessary, researchers can submit a request to modify the protocol for example the primary outcome and sample size calculation. And the steering committee and ethics committee have the authority to allow the modification of the plan.

18. 29 Please state why availability of data and materials is not applicable in this study.
Response: It does not contain any data in the protocol manuscript, so I declare that data and materials is not applicable in this study.

19. 30 Please give more detail in the manuscript about provisions for patients who suffer harm during the trial.
Response: Regardless of the cause, if the condition suddenly worsens during the trial and is accompanied by severe complications or serious adverse reactions, the trial will be terminated immediately, and prompt medical measures will be taken according to the subject's condition. The specialist will be prepared to deal with some harm during the study at any time, with treatments including oxygen therapy support, venous access and reasonable medication to maintain normal vital signs.

20. 31b Please clarify which authors will be eligible to be included as authors on the final trial report, and whether any professional writers will be utilized.
Response: Shuaipan Zhang, Qingguang Zhu, Chao Zhan, Wei Cheng, Xiao Ming fang, Min Fang, Lei Fang are eligible to be included as authors on the final trial report and no professional writers will be utilized.

21. 31c Please state any plans for public access to the protocol, dataset and code.
Response: The datasets generated and analyzed during the study will be available in the [Fig share] repository.
22. Please supply a model consent from as part of the manuscript or an additional document.
Response: I have provided Additional file 2 as a model consent from.

23. Please give more detail on the collection, laboratory evaluation and storage of biological specimens for possible future use.
Response: There is no collection, laboratory evaluation and storage of biological specimens.

**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