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Peer Review File

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Comments from Reviewer A

Comment 1: *From my point of view, some points still need to be revised. In particular, the discussion section lacks an actual scientific discussion of the results.*
Reply 1: Thank you for pointing this out. The reviewer is correct, we reconsidered the discussion section according to the Reviewers' feedbacks and modified our text as advised.

Comment 2: *Introduction*
Line 101 ff: The definition of post-COVID is not correct. It is rather to be defined as disease states that last longer than 3 (UK NICE) or at least 2 (WHO) months after a COVID-19 disease and cannot be explained by other circumstances. Long COVID is also usually defined differently in terms of time.
Reply 2: Thank you. As suggested by the Reviewer, we have described post-COVID according to the WHO definition. Changes in the text: "Post-COVID-19 can be defined as a condition among confirmed and recovered SARS-CoV-2 infected patients. Post-COVID-19 occurs usually 3 months after the diagnosis of COVID-19 infection and lasts at least 2 months and cannot be explained by other alternative diagnosis or condition."

Comment 3: *Methods*
Lines 146 ff.: The inclusion criteria are not entirely clear to me. Did all of the listed factors have to be present? If so, the ratio of the need for sleep disorders for pulmonological rehabilitation is not clear to me.
Reply 3: Thank you for pointing this out. We agree with this comment. Therefore, we have refined and clarified our criteria and for an easier readability listed in a table. Changes in the text: "Patients were involved at least 6 weeks after a negative PCR test result according to our criteria. Participants met the criteria were invited to the rehabilitation programme through their pulmonologists (Table 1.)."

Table 1: List of the criteria for enrolment

Inclusion criteria	Exclusion criteria

Individual 18 years or older	Unstable cardiovascular disease (uncontrolled high blood pressure (>140/90 mmHg), cognitive heart failure, angina NYHA* Class III-IV, etc.)
Can understand oral and written trial information	Severe rheumatic or orthopedic disease, which limits the freedom of movement
Previous diagnosed COVID-19 infection (≥3 months)	Mental illness
Weakness and/or reduced physical performance expressed after 6 weeks of COVID-19 infection	Unstable diabetes
Constant dyspnea at rest or during light exercise	Exacerbation of pre-existing chronic disease

*NYHA= New York Heart Association

Comment 4: *In my opinion, the description of the rehabilitation programme contains parts for discussion.*
Reply 4: Thank you. We agree with this and have incorporated your suggestion throughout the discussion. Changes in the text: As we refined the whole discussion, we used track changes to make the changes visible.

Comment 5: *Troponin THS presumably means "high sensitive". As this is an abbreviation, it should be explained the first time it is mentioned.*
Reply 5: Thank you. We corrected it.

Comment 6: *Results*
I recommend rewording lines 274 to 276 for better readability.
Reply 6: Thank you. As suggested by the Reviewer, we have rephrased the lines. Changes in the text: “To analyse the differences of continuous variables between the two groups we used Mann-Whitney test Frequency differences of categorical variables were tested by Fisher’s exact test.”

Comment 7: *The prevalence of COPD is surprising. Either all former smokers have COPD or there are several AT3 deficiencies? Was it permissible for COPD to be diagnosed after COVID-19? If so, post-infectious bronchial hypersensitivity would also be possible. Other listed comorbidities and symptoms are also more common post COVID, such as hypertension and anxiety.*
Reply 7: Thank you. We listed studies connected to COPD disorders and added to our article.

Comment 8: *The intended meaning in lines 301 to 302 is not clear to me. I recommend rephrasing.*

Reply 8: Thank you. As suggested by the Reviewer, we have rephrased the lines.

Comment 9: *Discussion*

Line 328: The word 'in' seems wrong.

Reply 9: Thank you. We corrected it.

Comment 10: *Line 337: The connection in the discussion of the study results with vaccination is unclear and should be explained in more detail.*

Reply 10: Thank you. We agree with the reviewer's assessment. Accordingly, throughout the manuscript, we have revised the paragraph about the vaccination and its connection to our study.

Changes in the text: "Studies showed that after a COVID-19 infection, vaccination can decrease in the odds of post-COVID. Vaccination as part of prevention can be beneficial not only against SARS-CoV-2 pathogen, but also may be advantageous to avoid serious post-COVID condition. The tendency of cumulative vaccine uptake of at least one vaccine in our study population was similar to the uptake in the total Hungarian population (cumulative uptake varied during the period, from 30% to 65.2%), however not only the authorized adenovirus vector or mRNA COVID-19 vaccines were in use in Hungary, we cannot detect any connection between the vaccination and the severity of post-COVID condition. Despite the fact, the importance of vaccination and participating in vaccination programmes are well known and highly recommended."

Comment 11: *The discussion is long, but is less a critical reflection on its own findings than a repetition of them and a review of the data so far. I recommend that, where appropriate, more attention be paid to confounders and methodological strengths and weaknesses of one's own results and those of other studies.*

Reply 11: Thank you. We agree with this and have incorporated your suggestion throughout the refining of the manuscript's discussion section.

Comment 12: *Lines 371 ff: Was interval training used in the current study? At least that is not what is described in the methods. Or is it seen as an improvement of one's own approach? The connection to the study results is not clear to me.*

Reply 12: Thank you for pointing this out. We agree with this comment. As planning the rehabilitation programme we would like to compare benefits of the low-intensity training and the interval training. In our study we only used the low-intensity training. That is why we removed the interval training from the manuscript.

Comment 13: *Line 389 ff: In the context of post-COVID, one cannot speak of long-term results at 2 months.*
Reply 13: Thank you for pointing out. We used the word "extant". Changes in the text: "In our 2-month follow-up we detected the extant beneficial effects of regular exercises."

Comment 14: *Line 423 f: Since more than half of the patients had COPD or asthma (cf. Fig. 1), the results should also be critically questioned as to whether the comorbidities were mainly influenced positively.*
Reply 14: Thank you. We agree with the Reviewer opinion, however one of our exclusion criteria was exacerbation of a chronic disease.

Comment 15: *Line 430-433: This is a result, not a discussion. And it is not mentioned in the results section at all.*
Reply 15: Thank you for pointing out. We replaced the lines to the result section.

Comment 16: *Line 452: The abbreviation RCT is not necessary for the study, since it is not used later.*
Reply 16: Thank you. We removed it.

Comment 17: *Points that must necessarily be discussed in the context of the present study are: a relevant proportion of the patients had a severe illness, including ICU. Thus, a post-ICU syndrome is also conceivable, which can also be rehabilitated.*
Reply 17: Thank you for pointing out the importance of ICU. We added some study result connected to ICU syndrome.

Comment 18: *Points that must necessarily be discussed in the context of the present study are*: *with several million patients with post-COVID syndrome, such a rehabilitative approach must be viewed critically from an allocation point of view.*
Reply 18: Thank you. You have raised an important point here. However, we believe that, in-patient rehabilitation is necessary in severe cases, however telerehabilitation can be a beneficial method of the post-COVID rehabilitation.

Comment 19: *Points that must necessarily be discussed in the context of the present study are*: *a control group is missing.*
Reply 19: Thank you for pointing this out. We agree that this is an important consideration, our study had no control group, because of the ethical dilemma our study is quasi-experiments study.

Comment 20: *Points that must necessarily be discussed in the context of the present study are*: *Even though post-exertional malaise or ME/CFS are rather rare sequelae of COVID-19, it should be addressed that they need to be diagnosed and the rehabilitative approaches are fundamentally different.*
Reply 20: Thank you. We have added the suggested content to the manuscript according to the CDC definition and report.

Comment 21: *Table 3: The usefulness of a statistical comparison of e.g. heart rate before and after exercise seems questionable to me. An increase in heart rate under stress is a physiological adaptation and does not need to be tested statistically.*
Reply 21: Thank you for pointing this out. The Reviewer is correct, and we have removed the table.

Comments of Reviewer B

Comment 1: The title is adequate however the vernacular "effectiveness" and "complex" used within the prose are ill-defined. The abstract is summarized fairly well written. The list of keywords is adequate. I found the aim/purpose of the study to be well-defined. Although the authors report that the study has been approved by the Ethical committee as appropriate, they did not provide the approval of IRB# In addition, it is unclear whether this study was registered before first enrollment (must provide this information).
Reply 1: Thank you. We appreciate the reviewer's feedback. We added the IRB number from the Ethical Statement.
Changes in the text: "Institutional Review Board (IRB) of the Semmelweis University registration number 160.1/2021"

Comment 2: The study design and data quality does carry weight. The results are presented adequately; however, the section is lengthy and verbose; I suggest modifying the section with major revisions and compressing them by using graphs/ figures/tables for improved clear communication of results. Otherwise, other included figures/tables are appropriate. The discussion is adequately written with respect to the authors' findings in terms of reported results. The authors did a nice job of avoiding repetitions and presentations of results avoided in the discussion. However, the opening paragraph is unnecessary as it may appear repetitious.
Reply 2: Thank you. We reorganized the context of our manuscript.

Comment 3: All aspects of the manuscript presented were relevant to the study. The limitations were discussed, and references were up-to-date, reflecting a thorough literature search. Finally, written English with appropriate style and grammar was also present. Overall, I found that the study does convey some degree of importance to the field of pulmonary rehabilitation. However, new phenomena or concepts that would add significant value to current understanding are weak, but they contribute modestly to clinical application concerning COVID-19.

Reply 3: Thank you for pointing out. We rebuilt our section of Discussion.

Comment 4: Title: [Pg.1, Lines 1-2] please consider re-writing the title in order to catch readers' attention/interest with clarification of what authors are insinuating by the "effectiveness"… what are you claiming? In other words, what do you wish to communicate with the "effectiveness" aspect of this rehabilitation protocol?

Reply 4: Thank you. Changes in the text: "Cardiopulmonary rehabilitation programme improves physical and mental health and quality of life in post-COVID syndrome"

Comment 5: Introduction: [Pg.3, Line 96] what is "complex" rehabilitation meant? Although the term appears to have vaguely alluded towards the conclusion of the introductory section, it is rather UNCLEAR; please define the term.

Reply 5: Thank you for pointing it out. Under the word complex we rather meant comprehensive.

Comment 6: Methods: [Pg.2, Lines 142-143] please spell out the months rather than using numerical dates (e.g. "January" as opposed to "01"); IRB approval# should also be reported. Overall, I found the prose in the methods to be extremely wordy; there are ways to convey all of the detailed methodologic details using tables/figures (e.g. "Inclusion/Exclusion" criteria); I suggest modifying this section to capture the readers' attention otherwise--as it is written--it is overly verbose with a high probability of losing readers' interest.

Reply 6: Thank you. We added the IRB number to this section as well and organized the criteria into a table.

Comment 7: Results: [Pgs.6-7, Lines 273-18] this section should convey the results only and in a manner with heightened readability and understanding; this is usually achieved by creatively using graphs depicted in figures/tables; suggest condensing the section by paraphrasing and deleting all unnecessary wording and communicate the findings illustratively.

Reply 7: Thank you. We think this is an excellent suggestion. We added the data to

tables.

Comment 8: Discussion: [Pg.10, Line 407] are there any other reports or data in the literature regarding the concepts of a "complex rehabilitation" program? Is there a consensus on a substantiated conceptual definition? If so, what is the underlying definition? Authors are suggested to clarify this in this part of their discussion, as previously mentioned.
Reply 8: Thank you for pointing out. Under the word "complex" we understand comprehensive.

Comment 9: [Pg.8, Lines 321-331] it is unnecessary to re-iterate what was already conveyed in the previous sections regarding results and methods. Perhaps one or two sentences are sufficient since the information is being repeated.
Reply 9: Thank you for this suggestion. We removed the unnecessary parts.

Comment 10: [Pg. 10, Lines 434-439] suggest strengthening the summary paragraph by re-iterating what was substantiated from the study based on your results.
Reply 10: Thank you. We have reiterated the suggested content in the manuscript.

Comment 11: Conclusion: [Pg.10, Lines 442-447] the abstract clearly states the "conclusion" succinctly and coherently, however in the main text, the conclusion paragraph wording is awkward; suggest re-wording to convey a final key point to the study's findings and for better readability.
Reply 11: Thank you for pointing out, we rewrote the conclusion section.

Comment 12: Limitations: [Pg.11, Lines 455-458] the limitations should be merely stated without a defense statement. The fourth point is unnecessary. Place the "Limitations" paragraph as the final paragraph of the body before the "Conclusion"
Reply 12: Thank you. We replaced the limitation section according to your suggestion.

Comment 13: Abbreviations: [Pg.11, Line 474] using a separate section at the end of your manuscript, list all abbreviations in capitalized letters on the LEFT column followed by the actual spelling of the abbreviated words on the RIGHT column as they appear in ORDER throughout the manuscript; use the heading "LIST OF ABBREVIATIONS."
Reply 13: Thank you for pointing out. We created the list of abbreviations.

Comment 14: Figures/Tables: Why didn't authors consider using "box & whisker

plot" graph for reporting inter-quartiles?
Reply 14: Thank you, unfortunately we have never used this method of graphics creation.

Comments of Reviewer C

Comment 1: Line 50: Suggest changing semi-colon to colon
Reply 1: Thank you. We changed it.

Comment 2: Lines 72-73 (last sentence of conclusions in abstract): I strongly disagree with this statement. Specifically, I disagree with the term "all". All patients would not benefit from cardiopulmonary rehabilitation as many experience post-exertional symptom exacerbation or post-exertional malaise. Need to mention screening for PESE and PEM prior to starting cardiopulmonary rehab.
Reply 2: Thank you for pointing this out. We rephrase our statement.

Comment 3: Line 104: Sentence beginning with "According to a US study..." needs rephrasing. I suggest "According to a US study, the prevalence of post-COVID syndrome ranges from 10% to 35% meaning that only 65% of patients returning to their previous state of health in 14-21 days after a positive COVID test."
Reply 3: Thank you for your suggestion, we rephrased it.

Comment 4: Line 106 - Sentence beginning with "Causes can be varied": I would suggest changing to "Causes are thought to be varied" since we do not know what causes long COVID yet
Reply 4: Thank you. Thank you for your suggestion, we changed it.

Comment 5: Paragraph beginning on Line 116: I have issues with this paragraph. While I have not made it through the rest of the paper yet, there is no discussion about PESE and PEM which are major considerations when suggesting treating long COVID with things like physiotherapy. Graded exercise approaches have been contraindicated in individuals with long COVID meaning that the screening for PESE and PEM are ESEENTIAL prior to starting any rehabilitation program. This paragraph makes it seem like patients should just start cardiopulmonary rehab ASAP when this may actually be harmful.
Reply 5: Thank you for pointing this out. Our physical examination before the enrolment is suitable for screening for PESE and PEM, however we didn't involve the DePaul Post-Exertional Malaise Questionnaire, which we intend to use in the future for more safety.

Comment 6: First sentence starting on Line 131: Again, recommending cardiopulmonary rehab for all symptomatic long COVID patients is not appropriate. Patients need to be screened for PESE and PEM. Also, having "appropriately trained professionals" casts a pretty wide net. Appropriately trained professionals trained in what?
Reply 6: Thank you. We redefined the study group.

Comment 7: Study design and population: I am wondering about time since COVID-19 infection? You need to include this detail for the reader to know that you actually recruited participants who met the diagnostic criteria for long COVID versus individuals who perhaps weren't at the 3 month post-acute infection point and could have just experiences spontaneous recovery over the course of your rehab program. Also, it is concerning to me that one of your inclusion criteria was dyspnea at rest or with light activity... these individuals may be experiencing PESE or PEM and if you did not screen for this, your program could have been harmful to these individuals.
Reply 7: Thank you for pointing this out. Our physical examination before the enrolment is suitable for screening for PESE and PEM, however we didn't involve the DePaul Post-Exertional Malaise Questionnaire, which we intend to use in the future for more safety.

Comment 8: Process of the rehab program: You discuss how patients underwent medical testing. did this include screening for PEM or PESE? If not, this is a major red flag.
Reply 8: Thank you for your warning, however we did the strict examination, and the hole rehabilitation program was done under personal supervision. I truly believe that patient safety the most important during our study. Taking your highly appreciated advised we will add the DePaul Post-Exertional Malaise Questionnaire to our protocol for more safety.

Comment 9: Line 165 (start of discussion about the program): Again, I dont want to continue to say the same thing over and over but previous research has shown that graded exercise can be contraindicated in some individuals with long COVID if they are experiencing PESE or PEM. This is a major consideration that I feel was overlooked in this paper and is a cause for concern about the rehab program. Your program could have/may have created harm to some of the patients you enrolled.
Reply 9: Thank you. We highlighted our points in the manuscript.

Comment 10: Line 190: Program considered successful if patients completed 75% of

sessions... this doesn't make sense to me. Shouldn't the success of the program be determined based on whether patients' outcomes improved? Maybe "success" isn't the right word?

Reply 10: Thank you. We agree, we rephrased the text.

Comment 11: Line 191: Okay now we have the timing info on how far patients were from acute infection. This information needs to go in the study population section and also include minimum time since acute infection... if it was less than 3 months than technically not long COVID

Reply 11: Thank you for pointing this out. We clarified the time passed after the actual COVID infection.

Comment 12: Line 204 (6 minute walk test): Again, 6 MWT may be fine for some individuals with long COVID but I have personally interviewed many patients with long COVID who did a 6 MWT and then experiences symptom flares/exacerbations as they were not properly screened for PEM or PESE. There needs to be some sort of discussion included in this paper about screening for PEM or PESE (or why you didnt think it was necessary) if it's going to be published

Reply 12: Thank you again for your point. We answered this question as mentioned above.

Comment 13: Line 216 - Quality of life assessment: Im left wondering why you chose the COPD assessment test?

Reply 13: Thank you for your question. We found studies where CAT was used successfully for measuring the status of post-COVID patients. After your suggestion we removed it from our data, because we had other, more powerful data to prove our results.

Comment 14: Lines 262-271: How did you control for any comorbidities that were present? A high proportion had comorbidities so this is something that needs to be statistically controlled for.

Reply 14: Thank you. The comorbidities were under consideration to plan the individual exercises during the rehabilitation and controlled strictly, moreover acute exacerbation our untreated conditions were exclusion criteria.

Comment 15: Sentence beginning on Line 312: Needs rephrasing. I suggest: "With the improved physical and mental condition, an increased level of workload, significantly decreased symptoms, and improved quality of life were detected."

Reply 15: Thank you. We rephrased it.

Comment 16: Lines 323-324: You call it low intensity endurance training and to individuals who are not suffering for long COVID or experiencing PEM or PESE it may be. However failing to screen for PEM or PESE means that this "low endurance" activity may have caused more harm than good. While you say there were no adverse effects from the rehab program, I would encourage you to comment on screening for PESE or PEM (i.e. why you didnt do it, what impacts it may have had on your sample). Also, I think there should be some comment on what you considered an "adverse effect" (lines 330-331 and mentioned earlier in paper).
Reply 16: Thank you. We tried to highlight our point in this question, as mentioned previously.

Comment 17: Paragraph beginning on line 332: It doesn't make any sense to me to tie the finding from your study to vaccination improving symptoms. Needs revising.
Reply 17: Thank you. We did it.

Comment 18: Line 349: You say the mentioned study reinforces your conclusion... how? Need more information on the connection.
Reply 18: Thank you. We rethought the connection.

Comment 19: Paragraph beginning on line 350: Comparing your results to the Pang et al study isn't clear... first of all Pang's study sounds like the improvements in patients outcomes could have been from the "herbal medicine" they received which your patients didnt. The connection between these two studies is weak and should be revised to a different study.
Reply 19: Thank you. We removed this part from the discussion to lead the focus on our result more.

Comment 20: Paragraph beginning on line 366: This paragraph is dangerous to include in a paper about long COVID. It suggests that interval training is essential for the recovery of long COVID. However, research shows that this is sometimes the complete opposite with interval training and graded exercises causing more harm than good for long COVID patients. I would not include a paragraph like this. There needs to be major work done to the discussion to address the points I've highlighted above as well as discuss the current research on the effects of graded exercise/interval training on long COVID rehab.
Reply 20: Thank you for pointing this out. At the beginning of the rehabilitation we found some studies, which used interval training for post-COVID rehabilitation,

however in our study - considering our patients' conditions – we never used it. That is why we removed this part.

Comment 21: I agree with line 380-386. Then 387 comes in an says the opposite... in 380-386 its saying that breathing and diaphragm exercises and stretching improved outcomes. Then 387 swoops in and says that physical activity is needed... these conflict each other.

Reply 21: Thank you for pointing this out, we rethought the context and solved the conflict.

Comment 22: Lines 414-417: The paper is almost over and this is the first mention of an individualized approach to long COVID rehab. I agree with this but not for just the reasons you mention.

Reply 22: Thank you for your point, we explained our point in different way.