Istituto di Biochimica e Biologia Cellulare
Institute of Biochemistry and Cell Biology
Dipartimento di Organi di Senso
Sapienza Università di Roma

February 4, 2026
Dear Editors and Reviewers:
Re: Revised version of the manuscript ID diseases-4125379.

We express our gratitude to the editors and reviewers for their valuable and insightful feedback on our original submission. We have carefully considered each comment and suggestion, and as a result, we have made major and minor revisions to our article to address the reviewers' concerns. All changes were evidenced by yellow point-by-point. We hope that these changes have improved the manuscript and that the reviewers will find it suitable for publication in Diseases.

Point-by-point response to Comments and Suggestions for Authors

REVIEWER 1

This revised paper improved significantly. There remains only a few minor remarks:

1. line 107: change "show promise" into "are promising".
2. line 187: add "other" between "on the" and "hand".
3. lines 214-215: change "Hyperbaric Oxygen Therapy" into "HBOT" as this abbreviation was earlier explained (see lines 113-114).
4. line 242: do the authors mean all kind of oxygen (normobaric and hyperbaric) or only hyperbaric oxygen?

Response 1: as suggested we replaced line 107,187 and 214-215 and line 242 oxygen mean normobaric and hyperbaric.

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REVIEWER 2

The manuscript presents an interesting review of the effects of application of hyperbaric oxygen therapy on long COVID symptoms. It is an important topic and may be of interest, especially for clinicians. The review follows the PRISMA guidelines, methodology is presented.

Remarks:

I suggest a thorough linguistic check of the text to eliminate phrasing that sometimes is far from optimal and sometimes leads to erroneous statements; some examples are given below.

Figure 1. „removed” should not be underlined

Response: in Fig.1 ‘removed’ is not underlined.

Lines 182-206: This section could be written using a more precise language

Line 198: “being able to do things”, a more precise statement would be better

Line 199: ”had problems with not getting oxygen to their tissues”, it seems to be an overstatement; perhaps “insufficient oxygen supply”

Response: lines 182-206. This section was entirely rewritten as follows:

HBOT protocol. There were significant differences in HBOT treatment protocols among the several investigations included (see Tab.1). The methods of HBOT therapy vary throughout the studies (see Tab.1-2). The length of each session, the total number of sessions, and the timing of the therapy following a COVID-19 infection all depend on the pressure that is applied. The studies that used pressures usually more than 2.0 ATA and longer treatment plan had better results. On the other hands the studies that used lower pressures or did not treat people for as long did not produce promising findings. The interval between contracting COVID-19 and initiating HBOT varies across studies, making it difficult to compare the effects of HBOT. In conclusion, since a universal protocol for the managements of patients with post-COVID-19 sequelae using HBOT has not yet established, it is difficult to achieve an effective comparison among the different populations analyzed in the studies reported in our literature search.

Characteristics of Patients. The recruited patients in different studies were all quite different. Some studies included adult patients, while other included younger patients. In addition, the number of males and females in each trial varied. The COVID-19 symptoms patients experienced, when they first became ill, also differed among studies. Some patients referred severe symptoms, others milder symptoms. They also had other co-morbidities. The main problems that patients had after they got COVID-19 were different in each study. Several research focused on issues with thinking and feeling exhausted. Studies that looked at patients who still had problems with not getting oxygen to their tissues or problems with small blood vessels often had better results with HBOT

COVID-19 treatment. COVID-19 patients who experienced these issues were more likely to respond to therapy. Some studies looked at people of ages or genders but this was not done very often. The sample sizes for these studies by age or gender were just too small to make strong comparisons between subgroups, like age or gender. (see Tab.1-2). Across the studies included in this review, individual patient clinical characteristics were frequently unreported, with most articles providing only aggregate descriptions of symptoms that improved or not following HBOT. This heterogeneity in reporting, together with the lack of standardized outcomes measures and treatment protocols, substantially limits comparability across studies and increases the risk of bias. Consequently, while symptom-specific treatment effects may be inferred, universally generalizable conclusion cannot be drawn.

Outcome Results. The reported results were influenced by differences in measurements taken in different studies. Consistent changes in results can be observed based on subjects' self-reported information, such as their reasoning ability, level of fatigue, and level of well-being. Physical parameters, such as lung function tests and imaging studies, do not show significant changes after the use of HBOT. The fact that the trials [29, 35] are still ongoing and did not all follow up with the people for time could have also made it harder to figure out what the results really meant and to compare them to each other. Here we are looking at the effects of HBOT, and the results of HBOT can be different as we can see in the conclusions reported among Table 1 and 2. Hadanny et al. [24], van Berkel et al. [25], Robbins et al. [27], Zant et al. [28], Leitman et al. [30], Gonevski et al. [32] and Lindenmann et al. [33], Mrakic-Sposta et al. [39], Pan et al [40], and Jermakow et al. [41], all reported positive outcomes following HBOT in the patient cohorts, with statistically significant improvements observed in quality of life, cognitive abilities, attention, left ventricular systolic function, and physical fatigue. These outcomes pertain to symptoms that had worsened following COVID-19. Conversely, Kjellberg et al. [26] described high frequency of adverse

events following HBOT and D'Hoore et al [31] reported no significant differences in subjective symptoms, functional scores, and cognitive performance between any groups analyzed.

Design of the Study. One more cause of variability in stated results found was study design. Uncontrolled tests and observational studies reported favorable impacts of HBOT more often than did randomized controlled trials, especially those using placebo treatments. Inconsistencies across the literature were exacerbated by sample size constraints and methodical heterogeneity as well. Future research should prioritize well-designed, standardized studies with larger sample sized and clearly defined clinical and methodological parameters to adequately assess the efficacy of structured HBOT treatment protocols.

Line 207: "*Measurements of Results",* not an optimal phrase

Response: line 207. We replaced with 'Outcome Results'.

Lines 213/214: "HBOT is what we are observing here and the results of Hyperbaric Oxygen Therapy can be different", Please rephrase

Response: line 213-214. We rephrased with 'Here we are looking at the effects of HBOT, and the results of HBOT can vary.

Line 216: "*Approach of Study",* better „Design of the study"

Response: line 216. We replaced with 'Design of the study.

Please format References according to the journal style.

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REVIEWER 3

Major comment:

In this manuscript, Introduction and Methods appear to be well written. However, Results presentation is not sufficient. Table 1, 2, 2 are just lists of literatures. Readers hope to see summarized findings from these literatures. In Result section, authors wrote the process of literature search mostly, however, descriptions of actual findings and conclusions seem to be less. Please

summarize the information in the collected literatures and write in the text and show in any new Table, if possible.

It is preferable to summarize data in systematic sections, for example, (1) patients information (age sex, underlying disease, etc.) (2) condition of therapy (Oxygen pressure level, duration, frequency, etc.) (3) results, prognosis, complications, etc. From these information, preferable application of patients for HBOT, therapeutic condition of HBOT, any attention to use HBOT, should be discussed.

Response: Thank you for pointing this out. We agree with this comment. The Results section was completely reorganized, improved and rewritten (see text manuscript, lines 180-238).

Tables 1, 2 and 3 show three parts, Study Design, Number of Patients and Synopsis, in which the main results of these studies are highlighted. For a detailed analysis, please refer to the original papers and protocols (references). The choice to present the studies in this manuscript aims to identify a clinical orientation for the use and application of HBOT in a post-COVID-19 context. The discussion section examines the salient aspects.

In any case, several systematic works cited (see references section) focus precisely on these requests, and to avoid redundancy in the literature, and being a synthetic review, it was preferred not to duplicate this information.

Discussion contains lots of contents, but they are not arranged appropriately and not concisely written. Please separate the description topics in different paragraphs in appropriate order. In the present version, second paragraph is too lengthy. This should be separated into several paragraphs.

Response: Thank you for this suggestion. We arranged the Discussion section in 5 subheadings to define more concisely the manuscript. New paragraphs are:

Neurological Symptoms:

Actual application and potential role of HBOT:

Molecular mechanisms of COVID-19 acute phase:

What about long-COVID?

What could be future directions in therapy?

Response: In addition, several parts were concisely written: Lines 251-263, 277-280, 317-325.

Minor comments:

1. Abastract, Line 26: Use only “HBOT”, because this word has been defined earlier.
   We confirm
2. Line 68, 78, 99, and others: “COVID-19 infection” is wrong words, because “COVID-19” is an established name of an infectious disease. Use only “COVID-19”. “SARS-CoV2 infection” is correct.
   We corrected.
3. Introduction, line 93-97: Add reference for this description.
4. We added a reference.

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5. Introduction, line 107-112: Add reference for this description.
   We added a reference.

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Kind regards,

Federica Zoccali, Christian Barbato and Antonio Minni

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