**Philippine COVID-19 Living Clinical Practice Guidelines**
*Institute of Clinical Epidemiology, National Institutes of Health, UP Manila*
*In cooperation with the Philippine Society for Microbiology and Infectious Diseases*
*Funded by the Department of Health*

# EVIDENCE SUMMARY

## Should hyperbaric oxygen therapy be used in COVID-19 patients with hypoxemia?

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## RECOMMENDATION

**We suggest against the use of hyperbaric oxygen therapy for the management of COVID-19 patients with hypoxemia due to insufficient evidence.** *(Very low certainty of evidence; Weak recommendation)*

*Consensus Issues*
The potential for the use of hyperbaric oxygen therapy in COVID-19 is recognized based on some reported benefit and minimal harm. However, its large cost and limited availability are important factors to consider especially since the noted benefits are based on a singular trial with very low certainty of evidence. More clinical trials are thus needed before recommending its use in patients with COVID-19.

## PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of hyperbaric oxygen therapy for the management of COVID-19 patients *(Very low quality of evidence)*

*Consensus Issues*
The high cost of hyperbaric oxygen therapy must be considered before recommending its use for the treatment of COVID-19 infection. There is also limited availability of hyperbaric oxygen therapy machines in the Philippines. Its use may applied in the context of a clinical trial. The results of ongoing studies are needed to show the use of hyperbaric oxygen therapy for the treatment of COVID-19 infection.

## What's new in this version?

- We included one new open-label randomized controlled trial which looked at mostly surrogate outcomes
- There is still insufficient evidence to recommend use of Hyperbaric Oxygen Therapy (HBOT) in COVID-19 patients with hypoxemia

## Key Findings

Two interventional studies (non-randomized and randomized controlled trials) were included in this review update on the use of hyperbaric oxygen therapy (HBOT) among COVID-19 patients with hypoxemia. HBOT appears to have a tendency towards benefit in reducing need for mechanical ventilation (HR 0.26, 95% CI 0.07-0.98) and in increasing the proportion of patients successfully weaned from oxygen support (RR 6.33, 95% CI 2.15-18.62). The effects of HBOT on mortality, oxygen saturation, and clinical improvement scores were inconclusive given the wide confidence intervals. The intervention appears generally safe with only a few minor adverse events including claustrophobia (RR 1.60, 95% CI of 0.07-38.20) and ear pain (RR 4.81, 95% CI of 0.27-86.47) reported. The overall certainty of evidence was low because of non-randomization, imprecision, and presence of possible confounders.

## Introduction

Hyperbaric oxygen therapy (HBOT) refers to modalities used to deliver intermittent supplemental oxygen in airtight vessels with controlled pressures of compressed air. The addition of high pressure allows the elevation in arterial oxygen tension beyond that which can be reached with conventional (i.e., normobaric) 100% oxygen supplementation alone. Apart from its direct effect on enhancing oxygen diffusion in hypoxic tissues, the high arterial oxygen tension is suggested to have indirect cell-signaling effects on the downregulation of inflammation.[1] For these reasons, the use of HBOT in COVID-19 has been investigated in clinical trials to counteract the hypoxemic and pro-inflammatory states seen in severe cases.[2]

## Review Methods

A literature search was performed across PubMed, Scopus, WHO ICTRP, MedRxiv, and ClinicalTrials.gov on October 26, 2021, as an update to a previous search done on March 8, 2021. Included studies were those which investigated the use of hyperbaric oxygen therapy in COVID-19 patients requiring oxygen supplementation. Keywords used in the systemic search for relevant articles were “hyperbaric oxygenation”, hyperbaric oxygen therapy”, “HBOT”, “COVID-19”, “coronavirus disease”, and “SARS-CoV-2 infection”. Observational studies and review articles were excluded. Full search strategy is presented in Appendix 2.

## Results

The updated literature search yielded 78 new records after removal of duplicates. Screening of titles and abstracts followed by appraisal of individual full text articles resulted in the inclusion of one new trial. Compared to the previous non-randomized prospective trial included in the original review, the new study in this update provides better methodological quality as a randomized controlled trial.

The two studies included were both deemed to have serious risk for bias, the first for non-randomization and the other for having an open-label study design. Certainty of evidence was very low for the non-randomized trial by Gorenstein and colleagues [3] (n = 80) owing to wide confidence intervals leading to the inconclusive interpretation of results, and also since the results presented were still part of an interim analysis. Meanwhile, certainty of evidence for the randomized controlled trial by Petrikov and coworkers [4] (n = 90) was low due to lack of blinding and indirectness.

Only one study looked at mortality and need for ventilation.[3] Mortality was shown to be lower in the group which received HBOT (Perry/Baromed) 2.0 ATA for 90min daily for up to 5 sessions (2/20, 10%) compared to propensity-matched controls which received standard of care (16/60,

22%). After adjusting for possible confounders, the effect of HBOT on inpatient mortality appears inconclusive (HR 0.37, 95% CI 0.10-1.37). In the same trial, the need for mechanical ventilation was lower in the HBOT group (2/20, 10%) compared to the control group (18/60, 30%). Based on very low-quality evidence, HBOT appears to have a tendency towards benefit in terms of reducing need for mechanical ventilation (HR 0.26, 95% CI 0.07-0.98).

The other study [4] showed more patients being successfully weaned from respiratory support among those given intermittent sessions of HBOT (Sechrist 2800) 1.4-1.6 ATA for 40min a day (19/24, 79.2%) compared to those who received standard of care alone (3/24, 12.5%).[4] HBOT appears to have definite benefit in terms of increasing the rate of weaning from respiratory support (RR 6.33, 95% CI 2.15-18.62) based on moderate certainty of evidence. In the same study, mean improvement in oxygen saturation measured at day 1 and day 14 was found to be significant in the HBOT group (MD 4.20, 95% CI 1.98-6.42) but not in the control group (MD 0.80, 95% -1.46-3.06). Comparing mean oxygen saturation at day 14 between HBOT and control, significant improvement was found only in the HBOT group (MD 2.70, 95% CI 0.72-4.68). Certainty of evidence for this outcome was assessed to be low because of indirectness as the analysis included both hypoxemic and non-hypoxemic patients. Analysis of clinical scores at baseline and after day 10 showed significant improvement in the HBOT group when compared to standard of care using the National Early Warning Score 2 (NEWS2) Score (MD -2.80, 95% CI -3.84 to -1.76) and the WHO Ordinal Scale for Clinical Improvement (OSCI) Score (MD -0.90, 95% CI -1.26 to -0.54) based on low certainty of evidence. Minor adverse events associated with HBOT included claustrophobia (RR 1.60, 95% CI 0.07-38.20) and ear pain (RR 4.81, 95% CI 0.27-86.47).[4]

## Evidence to Decision

Access to hyperbaric chamber therapy remains limited in the Philippines. Some institutions which offer outpatient sessions charge Php 1,500- 6,500 per session. Further well-powered studies may be needed to justify the cost of five to eight sessions of HBOT as therapy for COVID-19. Nevertheless, given the current published data on its efficacy and safety, it may be applied in the context of a clinical trial or for compassionate use.

## Recommendations from Other Groups

There has been no follow up to the position statement released by Undersea and Hyperbaric Medical Society and American College of Hyperbaric Medicine which was last updated on August 22, 2020.[5] The said document did not give specific recommendations for or against the use of HBOT among patients with COVID-19, but rather advocated for well-designed clinical trials on the topic and encouraged well-documentation whenever it is used off-protocol. There are still no recommendations on the use of HBOT in COVID-19 treatment guidelines from the World Health Organization, United of States National Institutes of Health, and Infectious Disease Society of America to date.[6–8]

## Research Gaps

Previous clinical trials on HBOT done among non-COVID patients have attempted sham treatment (i.e., being placed in an airtight container at 1.2 ATA) as control in an attempt to remove a possible placebo effect of being placed inside a chamber. Randomized clinical trials with hard outcomes such as mortality and need for mechanical ventilation are still ongoing. Since the initial review on this topic, three new trials have been registered, one study has been terminated, and one has been completed but with unreleased results. We currently await the results of ten clinical trials which may potentially change the consensus decision on the use of this therapy for COVID-19.

## References


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[8] Adarsh Bhimraj A, Morgan RL, Hirsch Shumaker A, Lavergne V, Baden L, Chi-Chung Cheng V, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. Infectious Diseases Society of America. 2021. Available from: www.idsociety.org/COVID19guidelines.

## Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7)

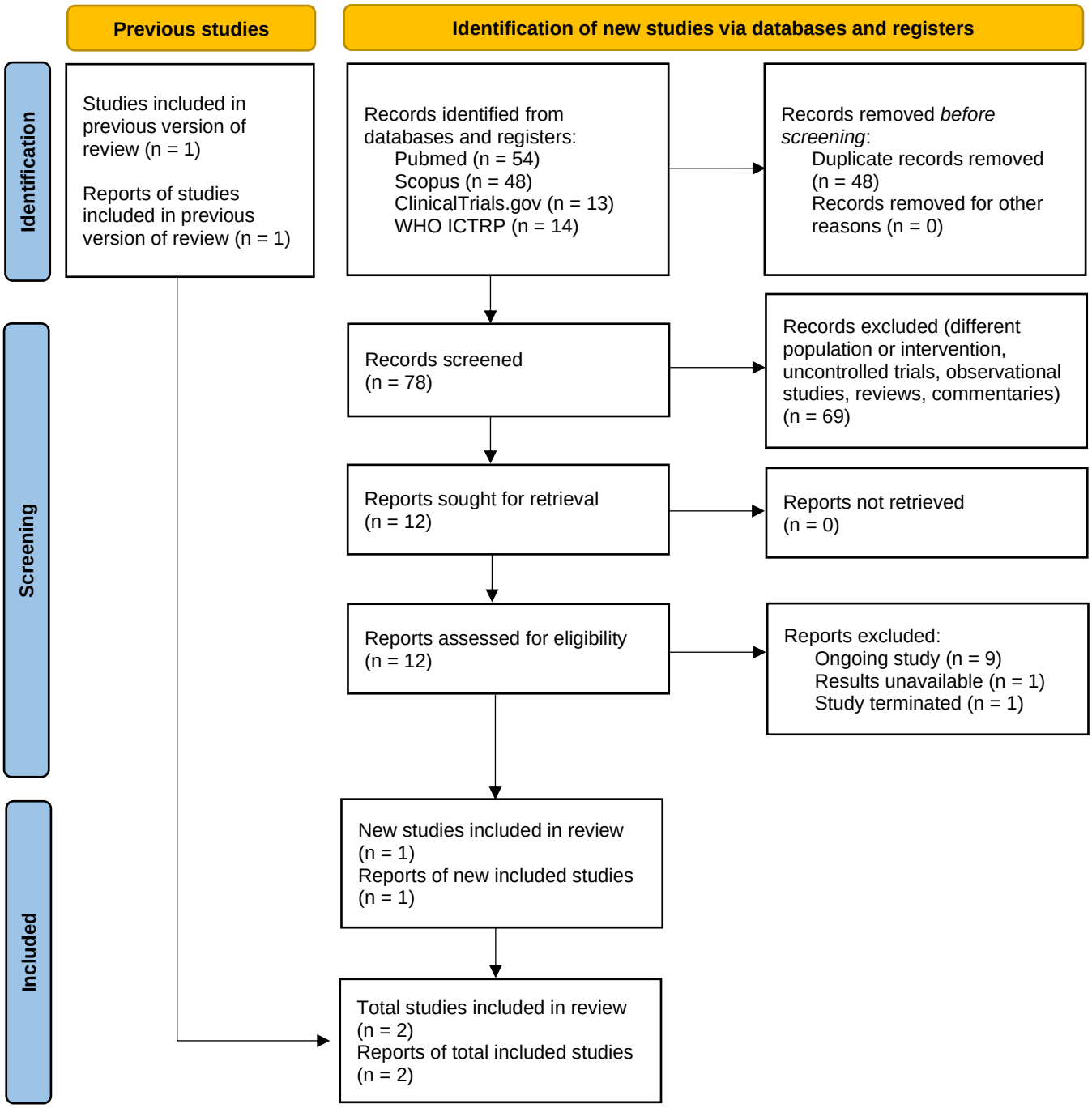
| FACTORS | JUDGEMENT | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|---|---|
| **Problem** | No | Yes (5) | | | | • Conventional respiratory support for patients with low oxygen saturation are effective in improving hypoxemia; but a number of patients still progress to need mechanical ventilation. |
| **Benefits** | Large (1) | Moderate (1) | Small (4) | Uncertain (1) | | • HBOT appears to have significant benefit in terms of increasing rates of weaning from respiratory support, increasing oxygen saturation, and improving clinical scores. |
| **Harm** | Large | Small (7) | Uncertain | | | • There are reports of minor adverse events (2-7%) such as claustrophobia and ear pain. No major adverse events were directly attributed to HBOT. |
| **Certainty of Evidence** | High | Moderate | Low (5) | Very low (2**)** | | |
| **Balance of effects** | Favors drug (3) | Does not favor drug (2) | Uncertain (2) | | | • Potential benefits outweigh harms, however cost, which was not mentioned in both studies, must be considered in our context. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Values** | Important uncertainty or variability (5) | Possibly important uncertainty or variability (1) | Possibly NO important uncertainty or variability (1) | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost (6) | Moderate Cost (1) | Negligible cost | Moderate savings | Large savings | • The cost of a session ranges from Php 1,500 to 6,000. The protocols used in most studies cited use 5 to 8 sessions. The direct cost is estimated to be between Php 7,500 to 48,000. |
| **Certainty of evidence of required resources** | No included studies (6) | Very low | Low (1) | Moderate | High | | |
| **Cost effectiveness** | No included studies (2) | Favors the comparison (2) | Does not favor either the intervention or the comparison (2) | Favors the intervention (1) | | | |
| **Equity** | Uncertain (1) | Reduced (5) | Probably no impact | Increased (1) | | | |
| **Acceptability** | Uncertain (3) | No (3) | Yes (1) | | | | |
| **Feasibility** | Uncertain (2) | No (4) | Yes (1) | | | | |

## Appendix 2. Search Yield and Results

| Database or Register | Query String | Total Results | Studies Included in Previous Review | New Studies |
|---|---|---|---|---|
| Pubmed (database) | ("COVID-19"[Mesh] OR (COVID-19)) AND ("hyperbaric oxygenation"[MeSH Terms] OR hyperbaric oxygen therapy OR HBOT) | 55 | 1 | 54 |
| Scopus (database) | TITLE-ABS-KEY(Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection) | 49 | 1 | 48 |
| ClinicalTrials.gov (register) | (Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection) | 141 | 1 | 13 |
| WHO ICTRP (register) | (Hyperbaric Oxygen Therapy OR Hyperbaric Oxygenation OR HBOT) AND (COVID-19 OR Coronavirus disease OR SARS-CoV-2 Infection) | 15 | 1 | 14 |
| MedRxiv | Hyperbaric oxygen AND COVID | 0 | 0 | 0 |

## Appendix 3. Prisma Flow Diagram



## Appendix 4. Characteristics of Included Studies

| Study ID | Study Design | Setting | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|---|
| Gorenstein 2020 | Non-randomized trial with propensity matched controls | New York, United States | COVID-19 patients with room air SpO2 <93% (n = 80) Excluded: pregnant, had pneumothorax, had positive troponin | HBOT (Perry/ Baromed) 2.0 ATA for 90 min daily for up to 5 sessions in addition to standard of care | Propensity matched controls (based on risk factors for poor outcomes) admitted during the same period | Primary: mortality Secondary: need for mechanical ventilation, days on mechanical ventilation |
| Petrikov 2021 | Open-label randomized controlled trial | Moscow, Russia | COVID-19 patients (n = 90) with moderate to severe disease severity assessed by chest CT Excluded: did not consent | HBOT (Sechrist 2800) 1.4-1.6 ATA for 40 min in addition to standard of care | Standard of care | Primary: SpO2 Secondary: clinical improvement scores (NEWS, OSCI) markers of oxidative stress (MDA, OCP, and apoptosis of lymphocytes) |

SpO2, peripheral capillary oxygen saturation; CT, computed tomography; HBOT, hyperbaric oxygen therapy; ATA, standard atmosphere unit; NEWS, national early warning score; OSCI, ordinal scale for clinical improvement; MDA, serum malone dialdehyde; OCP, open circuit potential.

# Appendix 5. GRADE Evidence Profile

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | hyperbaric oxygen therapy | normobaric oxygen or standard of care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality (follow-up: 16 days; assessed with: Inhospital mortality within the study period)** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | serious[b] | none | 2/20 (10.0%) | 13/60 (21.7%) | **Adjusted HR 0.37** (0.10 to 1.37) | **-- per 1,000** (from -- to --) | ⨁◯◯◯ Very low | |
| **Need for mechanical ventilation (follow-up: 16 days; assessed with: Required mechanical ventilation within the study period)** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | serious[c] | none | 2/20 (10.0%) | 18/60 (30.0%) | **Adjusted HR 0.26** (0.07 to 0.98) | **-- per 1,000** (from -- to --) | ⨁◯◯◯ Very low | |
| **Successful weaning from respiratory support (follow-up: 10 days; assessed with: Need for respiratory support (3-6 l/min oxygen support or noninvasive ventilation or high flow oxygen therapy) on day 4 and day 10 of admission)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [d] | not serious | not serious | not serious | none | 19/24 (79.2%) | 3/24 (12.5%) | **RR 6.33** (2.15 to 18.62) | **666 more per 1,000** (from 144 more to 1,000 more) | ⨁⨁⨁◯ Moderate | |
| **Change in oxygen saturation (follow-up: 14 days; assessed with: peripheral oxygen saturation measured at different point intervals)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [d] | not serious | serious | not serious | none | 96.1 | 93.4 | - | MD **+2.7 % SpO2** (+0.72 to +4.68)[e] | ⨁⨁◯◯ Low | |
| **Clinical improvement score (National Early Warning Score 2) (follow-up: 10 days; assessed with: Differences in summary scores based on respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, temperature and supplemental oxygen dependency on day 4 and day 10 of admission; Scale from: 0 to 20)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [d] | not serious | serious[f] | not serious | none | 3.2 | 0.7 | - | MD **-2.8 score** (-3.8 to -1.76)[g] | ⨁⨁◯◯ Low | |
| **Clinical improvement score (Ordinal Scale for Clinical Improvement) (follow-up: 10 days; assessed with: Differences in scores based on functionality on day 4 and day 10 of admission; Scale from: 1 to 8)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | hyperbaric oxygen therapy | normobaric oxygen or standard of care | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | serious [d] | not serious | serious[f] | not serious | none | 1.2 | 0.2 | - | MD **-0.9 score** (-1.26 to -0.54)[h] | ⨁⨁◯◯ Low | |

**Minor adverse events (claustrophobia) (follow-up: 14; assessed with: Proportion of patients who reported claustrophobia during the study duration)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious [d] | not serious | serious[f] | not serious | none | 1/57 (1.8%) | 0/30 (0.0%) | **RR 1.60** (0.07 to 38.20) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁⨁◯◯ Low | |

**Minor adverse events (ear pain) (assessed with: Proportion of patients who reported ear pain during the study duration)**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious [d] | not serious | serious[f] | not serious | none | 4/57 (7.0%) | 0/30 (0.0%) | **RR 4.81** (0.27 to 86.47) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁⨁◯◯ Low | |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## Explanations

a. non-randomized study

b. unadjusted subdistribution hazard ratio for time to death was 0.42 (p-value = 0.24, 95% CI of 0.10 to 1.79); adjusted subdistribution hazard ratio for inpatient mortality was 0.37 (p-value = 0.14, 95% CI of 0.10 to 1.37)

c. unadjusted subdistribution hazard ratio for time to mechanical ventilation was 0.30 (p-value = 0.09, 95% CI of 0.07 to 1.23); adjusted subdistribution hazard ratio for time to mechanical ventilation was 0.26 (p-value = 0.046, 95% CI of 0.07 to 0.98)

d. open-label trial

e. MD for HBOT +4.20 (95% CI 1.98, 6.42; p=0.0002), MD for Control +0.80 (95% CI -1.46, 3.06; p=0.70), MD for HBOT vs Control +2.70 (95% CI 0.72, 4.68; p=0.007

f. patients who did and did not require supplemental oxygen were both included in the analysis

g. MD for HBOT -3.20 (95% CI -4.23, -2.17; p<0.00001), MD for Control +0.70 (95% CI -0.46, 1.86; p=0.24), MD for HBOT vs Control -2.80 (95% CI -3.84, -1.76; p<0.00001)

h. MD for HBOT -1.20 (95% CI -1.54, -0.86; p<0.00001), MD for Control -0.20 (95% CI -0.60, 0.20; p=0.33), MD for HBOT vs Control -0.90 (95% CI -1.26, -0.54; p<0.00001)

## Appendix 6. Table of Ongoing Studies

| Study ID | Study Design | Population | Intervention | Comparator | Outcomes |
|---|---|---|---|---|---|
| Hyperbaric Versus Normobaric Oxygen Therapy for COVID-19 Patients (NCT04500626) | Randomized Controlled Trial | Adult COVID-19 patients in requiring 21%<FIO2≤100% to maintain saturation by pulse oximetry (SpO2) ≥90% | HBOT 2.0 ATA x 75 min | Normobaric oxygenation | 7-level COVID scale, hospital LOS, days with O2 supplementation, daily O2 flow values, ICU admission, ICU LOS, days on MV or NIV, major thrombotic events, sleep quality, fatigue, mortality, adverse events attributed to HBOT |
| Hyperbaric Oxygen for COVID-19 Patients With Moderate to Severe Hypoxemia (NCT04619719) | Randomized Controlled Trial | Adult COVID-19 patients with moderate to severe hypoxemia defined by a baseline supplemental oxygen requirement of 6 liters or higher within 24 h before enrollment | HBOT 2 ATA x 90 min x up to 5 treatments in addition to standard of care | Standard of care | Death from any cause 60 days after, time to mechanical ventilation, persistent symptoms, pulmonary function abnormality |
| Hyperbaric Oxygen Therapy (HBOT) as a Treatment for COVID-19 (COVID-19) Infection (NCT04343183) | Randomized Controlled Trial | Adult COVID-19 patients, O2 <90%, pO2 55-70 | HBOT | Standard of care | Decrease incidence of intubation by 30% or greater, decrease renal injury |
| Hyperbaric Oxygen Therapy Effect in COVID-19 RCT (NCT04358926) | Randomized Controlled Trial | Adult COVID-19 patients, room Air SpO2 <94% or PaO2/FiO2<300mmHg, at least one risk factor for bad prognosis of COVID-19 | HBOT 2.2 ATA x 60 min x 8 sessions in 4 days | Standard of care | SpO2, early warning score, CRP, WBC, IL-1, IL-2, IL-6, IL-10, TNF-a, PCT, ferritin, symptoms, IgM and IgG seroconversion, FEV1/FVC, time to recovery, requiring MV, time to negative PCR, mortality rate, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | barotrauma events |
| Hyperbaric Oxygen Therapy in Non-ventilated COVID-19 Patients (HBOT) (NCT04409886) | Randomized Controlled Trial | Adult COVID-19 patients, room Air SpO2 <94% or PaO2/FiO2<300mmHg, at least one risk factor for bad prognosis of COVID-19 | HBOT | None | PaO2/FiO2 (oxygenation index) |
| Management by Hyperbaric Oxygen Therapy of Patients with Hypoxaemic Pneumonia with SARS-CoV-2 (NCT04344431) | Randomized Controlled Trial | Adult COVID-19 patients need to maintain an oxygen flow rate less than or equal to 6 liters / min to obtain saturation by pulse oximetry (SpO2) greater than or equal to 92% or arterial gas with value PaO2 greater than 60mmHg | HBOT 1 session per day in addition to standard treatment | None | Time to normalized O2 requirement, hospital LOS, O2 needed, days on MV, mortality |
| Safety and Efficacy of Hyperbaric Oxygen for ARDS in Patients with COVID-19 (NCT04327505) | Randomized Controlled Trial | Adult COVID-10 patients with PaO2/FiO2 (PFI) below 200 mmHg and at least two risk factors for increased morbidity/mortality | HBOT 1.6-2.4 ATA 30-60 min | Standard of care | ICU admission, mortality, time-to-intubation, time-to-ICU, inflammatory response, OS |
| Compassionate Use of Hyperbaric Oxygen Therapy (NCT04386265) | Prospective observational | Adult COVID-19 patients | HBOT | None | Need for mechanical ventilation in COVID-19 patients, adverse events associated with HBOT |
| Effecacy and Safety of Hyperbaric Oxygen Therapy to Patients with Novel Coronavirus Pneumonia | Randomized Controlled Trial | Adult COVID-19 patients meeting severe criteria: RR >30 bpm, SpO2 ≤93%, PaO2/FiO2 ≤300, | HBOT 1.5 ATA group and HBOT 2.5 ATA group | Standard of care | Oxygenation index, activity endurance, IL-6, blood routine biochemical indicators, lung CT, microparticle, CRP |

| | | | | | |
|---|---|---|---|---|---|
| (COVID-19) (ChiCTR2000032011) | | significant progression of pulmonary lesions within 24-48 h on imaging | | | |
| Hyperbaric Oxygen Therapy for Hospitalized Patients with COVID-19 (U1111-1253-2793) | Randomized Controlled Trial | Adult COVID-19 patients with hypoxemia defined as SaO2 less than or equal to 94% | HBOT 2.0 ATA daily for 5 days | Hyperbaric chamber 1.2 ATA daily for 5 days | Number of days to defervescence, reduction in cough, SpO2, PpO2, days to respiratory improvement, mortality, outpatient treatment days |