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LIVING SYSTEMATIC REVIEW OF THERAPEUTIC OPTIONS FOR POST-COVID-19 CONDITION.

January 11th, 2023

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Living Systematic Review of Therapeutic Options for Post COVID-19 Condition

Washington, D.C.

11 January 2023

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PAHO/IMS/EIH/COVID-19/23-0001

Disclaimer

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. In recognition of the fact that there are numerous ongoing clinical studies, PAHO will periodically update this review and corresponding recommendations as new evidence becomes available.

Contents

Acknowledgment

This document was developed by Ariel Izcovich, Martin Ragusa, Fernando Tortosa, Sasha Peiris, and Ludovic Reveiz from the knowledge Translation Program, Department of Evidence and Intelligence for Action in Health and the Incident Management System for the response to COVID-19, Pan American Health Organization. It was strengthened with the valuable contributions of: Pedro Ordunez, Antony Duttine and Carmen Martinez from the Noncommunicable Diseases and Mental Health department, Pan American Health Organization and Sylvain Aldighieri Deputy Director of the Health Emergencies and Incident Management System for the response to COVID-19.

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Executive summary

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2. The World Health Organization (WHO) definition states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation. It can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and the quality of life. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others.

This review compiles the following evidence on potential therapeutic options for PCC. It includes all the identified clinical forms, symptoms, and manifestations of PCC for which an intervention was assessed in at least one randomized controlled trial (RCT). It is hoped this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of PCC, at both the individual and population levels, is based on the best available knowledge. This resource will be continually updated as more research is released into the public space.

Summary of evidence

All odd numbered tables (Table ES1 to ES13) present RCTs according to the reported PCC symptom and indicate the primary outcome measures used for each investigation and the level of certainty. The even numbered tables (Table ES2 to ES14) summarize the status of evidence for the 25 potential therapeutic options for PCC for which studies were identified through this systematic review.

PCC-related asthenia or fatigue

Table ES1. List of RCTs on interventions for PCC-related asthenia or fatigue with primary outcome measures and certainty (n = 13)

Intervention		Overall number of studies including the intervention, n=13	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Fatigue improvement (n of studies)	Functional capacity improvement (n of studies)	Strength improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Fermented food supplements	NEW	2		2					
1_MNA	NEW	1							
ADAPT_232 (adaptogens)	NEW	1			1				
Arginine_Vitamin C	NEW	1			1		1		
CQ10	NEW	1	1	1					
Cytoflavin	NEW	1			1				
Enzimes_Probiotics	NEW	1			1				
Hydrogen (nasal)	NEW	1			1	1			
Physical training	NEW	1	1				1		
Leronlimab	NEW	1		1					
tDCS	NEW	1			1			1	
Telerehabilitation	NEW	1	1		1	1			

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES2. Summary of findings on potential therapeutic options for PCC-related asthenia or fatigue (n = 12), as of 6 January 2023

	Intervention	Summary of findings
1	**1-MNA**	Uncertainty in potential benefits and harms. Further research is needed.
2	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
3	**Arginine + Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
4	**Coenzyme Q10**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Cytoflavin**	Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.
6	**Enzymes + probiotics**	Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.
7	**Fermented food supplements**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Hydrogen (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Leronlimab**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Physical training**	Uncertainty in potential benefits and harms. Further research is needed.
11	**Transcranial direct current stimulation (tDCS)**	tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
12	**Telerehabilitation**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined 12 therapeutic options for PCC-related asthenia or fatigue.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve fatigue. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Cytoflavin:** The results of one RCT suggest that cytoflavin may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Enzymes + probiotics:** The results of one RCT suggest that enzymes + probiotics may not improve fatigue. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of one RCT suggest that tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low because of imprecision. Further research is needed.

PCC-related dyspnea

Table ES3. List of RCTs of interventions for PCC-related dyspnea with primary outcome measures and certainty (n = 6)

Intervention		Overall number of studies including the intervention, n=6	HRQL improvement (n of studies)	Dyspnea improvement (n of studies)	Functional capacity improvement (n of studies)	Pulmonary function improvement (n of studies)	Radiological response (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Respiratory training	NEW	2	2	2		1			
ADAPT_232 (adaptogens)	NEW	1		1					
Endurance training	NEW	1	1	1					
High dose steroids	NEW	1		1			1	1	1
Treamid	NEW	1		1	1	1		1	

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES4. Summary of findings on potential therapeutic options for PCC-related dyspnea (n = 5), as of 6 January 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low. Further research is needed.
2	**Endurance training**	Endurance training may improve health-related quality of life (HRQL) and dyspnea. However, certainty of the evidence was low. Further research is needed.
3	**High dose steroids**	High dose steroids, compared to standard dose steroids, may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.
4	**Respiratory training**	Respiratory training may improve HRQL and dyspnea. However, certainty of the evidence was low. Further research is needed.
5	**Treamid**	Treamid may improve dyspnea and pulmonary function but may not improve functional capacity. Treamid may increase adverse events. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined five therapeutic options for PCC-related dyspnea.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may not improve dyspnea. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Endurance training:** The results of one RCT suggest that endurance training may improve dyspnea and HRQL compared to standard physiotherapy. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **High dose steroids:** The results of one RCT suggest that high dose steroids (prednisone 40 mg a day) may not improve dyspnea compared to standard dose steroids (prednisone 10 mg a day). However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

• **Respiratory training:** The results of two RCTs suggest that respiratory training may improve dyspnea and HRQL. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed.

• **Treamid:** The results of one RCT suggest that treamid may improve dyspnea and pulmonary function but may not improve functional capacity. However, certainty of the evidence was low because of imprecision. Further research is needed.

PCC-related neurocognitive symptoms

Table ES5. List of RCTs of interventions for PCC-related neurocognitive symptoms with primary outcome measures and certainty (n = 3)

Intervention		Overall number of studies including the intervention, n=3	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Cognitive improvement (n of studies)	Depression improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
HBO	NEW	1	1		1	1		
taVNS	NEW	1						
tDCS	NEW	1			1			

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES6. Summary of findings on potential therapeutic options for PCC-related neurocognitive symptoms (n = 3), as of 6 January 2023

	Intervention	Summary of findings
1	**Hyperbaric oxygen (HBO)**	HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.
2	**Transcutaneous auricular vagus nerve stimulation (taVNS)**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Transcranial direct current stimulation (tDCS)**	tCDS may not improve cognition. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of

clinical trials and observational studies. In this review, we identified and examined three therapeutic options for PCC neurocognitive symptoms.

• **Hyperbaric oxygen (HBO):** The results of one RCT suggest that HBO may improve HRQL. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Transcranial direct current stimulation (tDCS):** The results of one RCT suggest that tDCS may not improve cognition. However, certainty of the evidence was low because of imprecision. Further research is needed.

PCC-related olfactory and/or gustatory dysfunction

Table ES7. List of RCTs of interventions for PCC-related olfactory and/or gustatory dysfunction with primary outcome measures and certainty (n = 7)

Intervention		Overall number of studies including the intervention, n=7	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Olfactory symptoms improvement (n of studies)	Gustatory symptoms improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Olfactory training	NEW	3			3			
ADAPT_232 (adaptogens)	NEW	1			1			
Palmitoylethanolamide_Luteoli	NEW	1			1			
Steroids (nasal)	NEW	1			1			
Steroids	NEW	1			1			

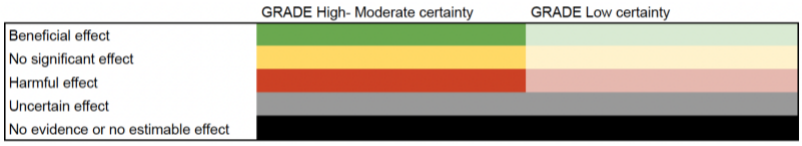


Table ES8. Summary of findings on potential therapeutic options for PCC-related olfactory and/or gustatory dysfunction (n = 5), as of 6 January 2023

	Intervention	Summary of findings
1	**ADAPT-232 (adaptogens)**	ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
2	**Olfactory training**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Palmitoylethanolamide + Luteolin**	Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.
4	**Steroids (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Steroids**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined five therapeutic options for PCC olfactory and/or gustatory dysfunction.

• **ADAPT-232 (adaptogens):** The results of one RCT suggest that ADAPT-232 may improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Palmitoylethanolamide + Luteolin:** The results of one RCT suggest that Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low because of imprecision. Further research is needed.

PCC-related cardiovascular system symptoms

Table ES9. List of RCTs of interventions for PCC-related cardiovascular system symptoms with primary outcome measures and certainty (n = 1)

Intervention		Overall number of studies including the intervention, n=1	HRQL improvement (n of studies)	Overall symptom improvement (n of studies)	Tachycardia improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Ivabradine	NEW	1			1		

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES10. Summary of findings on potential therapeutic options for PCC-related cardiovascular system symptoms (n = 1), as of 6 January 2023

	Intervention	Summary of findings
1	**Ivabradine**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC- related cardiovascular system symptoms.

• **The effects of assessed interventions are uncertain.**

PCC-related psychological distress

Table ES11. List of RCTs of interventions for PCC-related psychological distress with primary outcome measures and certainty (n = 1)

Intervention		Overall number of studies including the intervention, n=1	HRQL improvement (n of studies)	Depression improvement (n of studies)	Post traumatic stress disorder improvement (n of studies)	Psychologic distress improvement (n of studies)	Adverse events (n of studies)	Severe adverse events (n of studies)
Virtual reality	NEW	1		1	1	1		

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES12. Summary of findings on potential therapeutic options for PCC psychological distress (n = 1), as of 6 January 2023

	Intervention	Summary of findings
1	**Virtual reality-based interventions**	Virtual reality-based interventions may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC psychological distress.

• **Virtual reality-based interventions:** The results of one RCT suggest that virtual reality-based interventions may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low because of imprecision. Further research is needed.

PCC-related thromboembolic risk

Table ES13. List of RCTs of interventions for PCC-related thromboembolic risk with primary outcome measures and certainty (n = 1)

Intervention		Overall number of studies including the intervention, n=1	Mortality (n of studies)	HRQL improvement (n of studies)	VTE (symptomatic) (n of studies)	Major bleeding (n of studies)	Severe adverse events (n of studies)
Anticoagulants_Proph	NEW	1	1		1		

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table ES14. Summary of findings on potential therapeutic options for PCC thromboembolic risk (n = 1), as of 6 January 2023

	Intervention	Summary of findings
1	**Anticoagulants (prophylactic dose)**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to the WHO International Clinical Trials Registry Platform (ICTRP), multiple potential interventions are being assessed in hundreds of clinical trials and observational studies. In this review, we identified and examined one therapeutic option for PCC olfactory and/or gustatory dysfunction.

• **The effects of assessed interventions are uncertain.**

Changes since previous edition

• First version of the review.

Concluding remarks

• The Pan American Health Organization (PAHO) is continually monitoring ongoing research on any possible therapeutic options. As evidence emerges, PAHO will immediately assess and update its position, particularly as it applies to any special population subgroups such as children, expectant mothers, and those with immune conditions.

• PAHO is also mindful of the emerging differential impact of PCC on ethnic and minority groups and is continuously seeking data that could help in mitigating excess risk of severe illness or death in minority subgroups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID-19 illness.

• The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.

• Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on PCC has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Systematic review of therapeutic options for post COVID-19 condition

Background

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2 *(1, 2)*. The World Health Organization (WHO) definition states that these symptoms should be present after three months of the initial SARS-CoV-2 infection and last for at least two months with no other explanation *(2)*. It can affect anyone exposed to SARS-CoV-2, regardless of age or severity of acute infection. Many of the reported symptoms are debilitating and have a strong negative impact on mental health and the quality of life *(3)*. While most patients recover, some may experience multiple outcomes, with multiple organ systems affected simultaneously, including cardiovascular, mental, metabolic, renal, and others *(1, 4)*. Recommendations for the management of patients with PCC are continuously being developed and need to evolve as evidence of interventions effects becomes available(5).

In this review, we compiled the following evidence on potential therapeutic options for PCC. We included all the identified clinical forms, symptoms, and manifestations of PCC for which an intervention was assessed in at least one randomized controlled trial (RCT). We hope this information will support investigators, policymakers, and prescribers navigate the flood of relevant data to ensure that management of PCC, at both the individual and population levels, is based on the best available knowledge. We will endeavor to continually update this resource as more research is released into the public space.

Methods

We used the Living OVerview of Evidence (L·OVE; https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The latest version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website *(6)*.

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page, available from: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods. The repository is continuously updated, and the information is transmitted in real time to the L·OVE platform. It was last checked for this review on 6 January 2023. The searches covered the period from the inception date of each database, and no study design, publication status, or language restriction was applied.

Study selection

The results of the searches in the individual sources were de-duplicated by an algorithm that compares unique identifiers (database identification number, digital object identifier [DOI], trial registry identification number), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). Then, the information matching the search strategy was sent in real time to the L·OVE platform, where at least two authors independently screened the titles and abstracts yielded against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis and then decided about their inclusion.

Inclusion criteria

We aimed to find all available RCTs for potential therapeutic interventions for PCC with study designs that included head-to-head comparisons, or control groups with no intervention or a placebo. Target patient populations included both adults and children with PCC. We defined PCC as the continuation or development of new symptoms after COVID-19. We expanded the WHO PCC definition and decided not to exclude studies that included patients with less than two months of duration of symptoms and/or less than three months from the onset of symptoms *(7)*. We focused on comparative effectiveness studies that provide evidence on outcomes of crucial importance to patients (mortality, health-related quality of life [HRQL], and disease-specific symptoms).

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. If meta-analytical pooling is possible from retrieved evidence, we will do this to derive more precise estimates of effect and derive additional statistical power. No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). For baseline risks we used the mean risk in the control groups from included RCTs. For continuous outcomes, when possible, we calculated relative and absolute effects by estimating the proportion of patients with important improvement or deterioration following published guidance *(8)*.

For result interpretations and imprecision assessment we used a minimally contextualized approach that considers whether the 95% confidence interval (CI) includes the null effect, or, when the point estimate is close to the null effect, whether the 95% CI lies within the boundaries of small but important benefit and harm that corresponds to every outcome assessed *(9, 10)*.

We used the following absolute effects thresholds to define important benefits and harms: Mortality, +/-1%; HRQL improvement, +/-2%; Overall symptom improvement, +/-5%; Functional capacity improvement, +/-5%; Strength improvement, +/-5%; Fatigue improvement, +/-5%; Pulmonary function improvement, +/-10%; Radiological response, +/-10%; Cognitive improvement, +/-5%; Depression improvement, +/-5%; Olfactory symptoms improvement, +/-5%; Gustatory symptoms improvement, +/-5%; Tachycardia improvement, +/-5%; Venous thromboembolism (VTE) (symptomatic), +/-3%; Post-traumatic stress disorder improvement, +/-5%; Psychological distress improvement, +/-5%; Major bleeding, +/-3%; Severe adverse events, +/-3%; Adverse events, +/-5%.

For some interventions when we found significant heterogeneity, we performed subgroup analysis considering: 1) risk of bias (high/moderate vs low risk of bias); and 2) intervention characteristics (e.g., different doses or administration schemes). When we observed significant differences between subgroups, we presented individual subgroups' estimates of effect and certainty of the evidence assessment.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 1) *(11)*. The GRADE approach was used to assess the certainty of the body of evidence for every comparison on an outcome basis *(12)*.

Study selection, data extraction, and risk of bias assessment were performed, independently and in parallel, by two reviewers. Discrepancies were resolved by discussion.

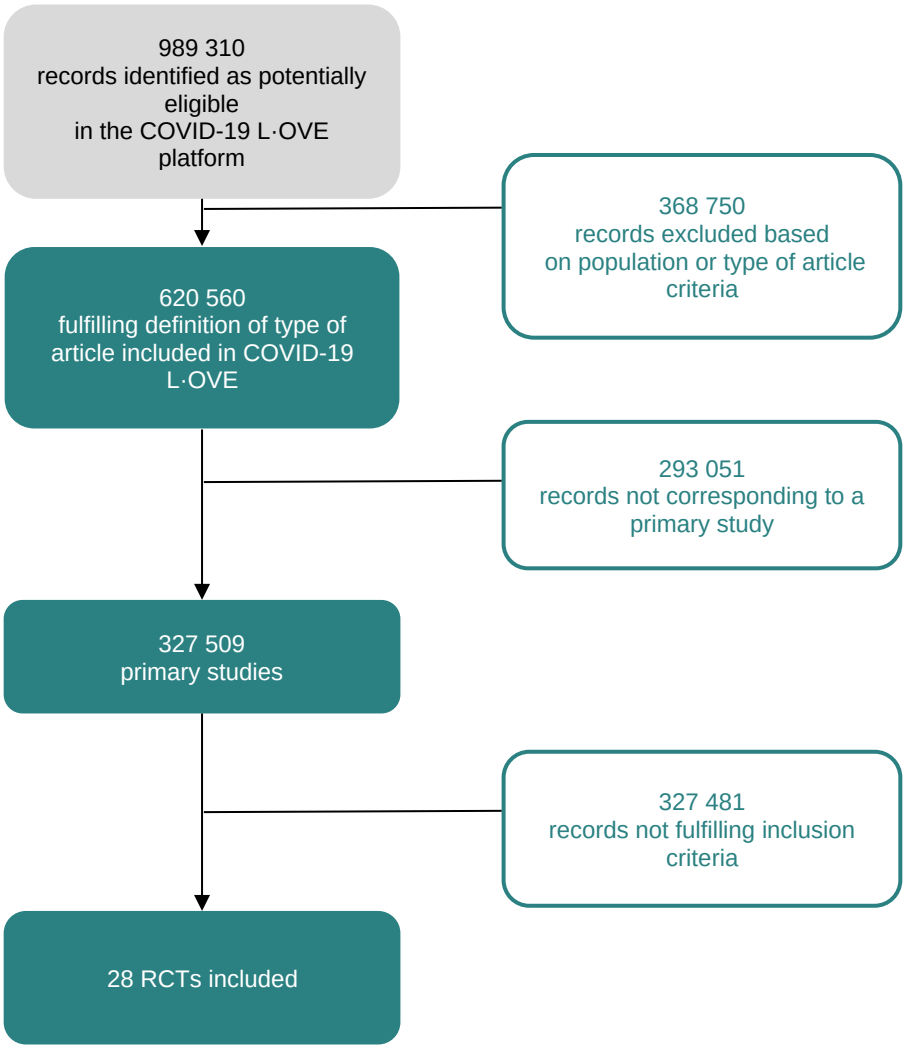
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Annex 1.

Results

Studies identified and included

The study identification and selection process is shown in Figure 1. A total of 28 RCTs were selected for inclusion. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs found high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. In general, follow-up was short. The risk of bias assessment of each RCT is presented in Table 1.

Table 1. Risk of bias of included RCTs

Study	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	Overall Risk-of-bias judgement	
						Mortality	HRQL, symptom specific outcomes
Vaira LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RC 4-7-2020 (Abdelalim AA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
Di Stadio	Low	Low	Low	Low	Low	Low	Low
Chudzik M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CITADEL	High	Some Concerns	Low	Some Concerns	Low	High	High
MICHELLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Zilberman-Itskovich	Low	Low	Low	Low	Low	Low	Low
Botek M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Jadhav KP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COLDSTER	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Oliver-Mas	Low	Low	Low	Low	Low	Low	Low
Nambi	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Di Stadio_2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hansen	Low	Low	Low	Low	Low	Low	Low
Tosato	High	Some Concerns	Low	Some Concerns	Low	High	High
Rathi	High	Some Concerns	Low	Some Concerns	Low	High	High
Bazdyrev	Low	Low	Low	Low	Low	Low	Low
King	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ICU-VR	High	Some Concerns	Low	Some Concerns	Low	High	High
ENO Breathe	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pires	High	Some Concerns	Low	Some Concerns	Low	High	High
McNarry	High	Some Concerns	Low	Some Concerns	Low	High	High
Srinivasan	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Moderate	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharaeva_Severe	High	Some Concerns	Low	Some Concerns	Low	High	High
Gaylis	High	Some Concerns	Low	Some Concerns	Low	High	High
Karosanidze	Low	Low	Low	Low	Low	Low	Low
Badran	Low	Low	Low	Low	Low	Low	Low
COVANOS	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVER	High	Some Concerns	Low	Some Concerns	Low	High	High

Main findings

PCC-related asthenia or fatigue

ADAPT-232 (adaptogens)

See Summary of findings Table A1, Annex 1

We identified one RCT including 99 participants in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve fatigue, relative risk (RR) 1.02 (95% CI 0.84 to 1.24); risk difference (RD) 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯

Cytoflavin

See Summary of findings Table A2, Annex 1

We identified one RCT including 200 patients in which cytoflavin was compared against standard of care. Our results showed:

- Cytoflavin may not improve fatigue, RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⊕⊕◯◯

Enzymes + probiotics

See Summary of findings Table A3, Annex 1

We identified one RCT including 200 patients in which enzymes + probiotics were compared against standard of care. Our results showed:

- Enzymes + probiotics may improve fatigue, RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Moderate certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

See Summary of findings Table A4, Annex 1

We identified one RCT including 47 patients in which tDCS was compared against standard of care. Our results showed:

- tDCS may not improve fatigue, RR 0.95 (95% CI 0.5 to 1.79); RD –2.4% (95% CI –22.8% to 36.4%); Low certainty ⊕⊕◯◯

PCC-related dyspnea

ADAPT-232 (adaptogens)

See summary of findings Table A5 in Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared against standard of care. Our results showed:

- ADAPT-232 may not improve dyspnea, RR 1 (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.7%); Low certainty ⊕⊕◯◯

Endurance training

See Summary of findings Table A6 in Annex 1

We identified one RCT including 60 patients in which endurance training was compared against standard physiotherapy. Our results showed:

- Endurance training may improve HRQL, RR 1.48 (95% CI 0.92 to 2.37); RD 21% (95% CI –3.4% to 60%); Low certainty ⊕⊕◯◯
- Endurance training may improve dyspnea, RR 2.03 (95% CI 0.98 to 4.21); RD 24% (95% CI –0.4% to 76%); Low certainty ⊕⊕◯◯

High dose steroids

See Summary of findings Table A7, Annex 1

We identified one RCT including 130 patients in which high dose steroids (prednisone 40 mg a day) was compared against standard dose steroids (prednisone 10 mg a day). Our results showed:

- High dose steroids may not improve dyspnea, RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11% to 13%); Low certainty ⊕⊕◯◯
- High dose steroids may not increase adverse events, RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯

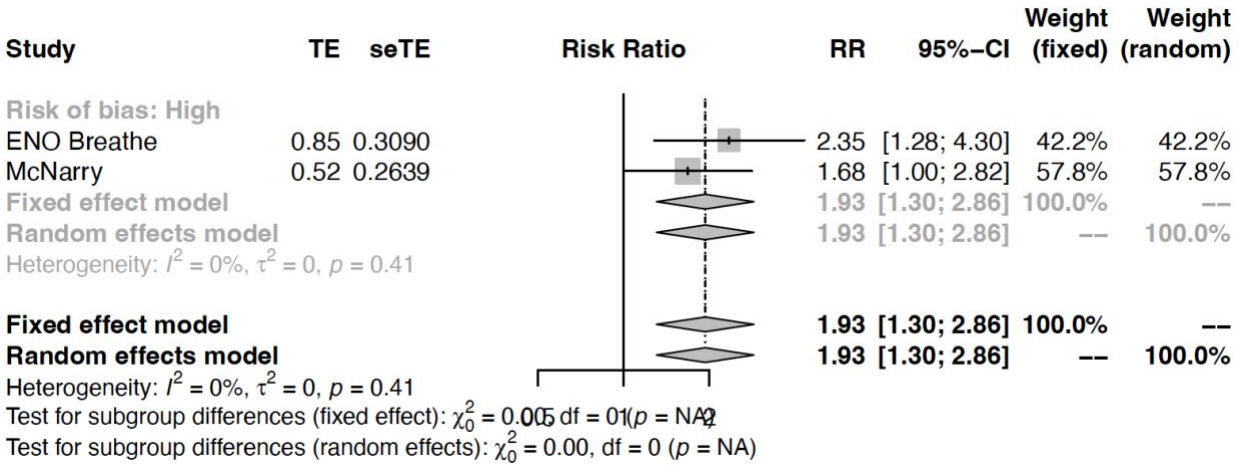
Respiratory training

See Summary of findings Table A8, Annex 1

We identified three RCTs including 271 patients in which different modalities of respiratory training were compared with standard of care. Our results showed:

- Respiratory training may improve HRQL, RR 1.93 (95% CI 1.3 to 2.86); RD 24.1% (95% CI 7.8% to 48.1%); Low certainty ⊕⊕◯◯ (see Figure 2)
- Respiratory training may improve dyspnea, RR 1.33 (95% CI 0.97 to 1.82); RD 12.3% (95% CI –1.1% to 30.5%); Low certainty ⊕⊕◯◯

Figure 2. HRQL in RCTs comparing respiratory training with standard of care for treatment of patients with PCC-related dyspnea



Treamid

See Summary of findings Table A9, Annex 1

We identified one RCT including 59 patients in which treamid was compared with standard of care. Our results showed:

- Treamid may improve dyspnea, RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⊕⊕◯◯
- Treamid may improve functional capacity, RR 1.1 (95% CI 0.64 to 1.9); RD 0.4% (95% CI 16.2% to 39.8%); Low certainty ⊕⊕◯◯
- Treamid may increase adverse events, RR 1.19 (95% CI 0.56 to 2.5); RD 5.5% (95% CI –12.7% to 43.6%); Low certainty ⊕⊕◯◯

PCC-related neurocognitive symptoms

Hyperbaric oxygen (HBO)

See Summary of findings Table A10, Annex 1

We identified one RCT including 73 patients in which HBO was compared with standard of care. Our results showed:

- HBO may improve HRQL, RR 1.3 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⊕⊕◯◯

Transcranial direct current stimulation (tDCS)

See Summary of findings Table A11, Annex 1

We identified one RCT including 47 patients in which tDCS was compared with standard of care. Our results showed:

- tDCS may not improve HRQL, RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⊕⊕◯◯

PCC-related olfactory and/or gustatory dysfunction

ADAPT-232 (adaptogens)

See Summary of findings Table A12, Annex 1

We identified one RCT including 99 patients in which ADAPT-232 was compared with standard of care. Our results showed:

- ADAPT-232 may not improve olfactory symptoms, RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯

Palmitoylethanolamide + Luteolin

See Summary of findings Table A13, Annex 1

We identified one RCT including 126 patients in which palmitoylethanolamide + luteolin was compared with standard of care. Our results showed:

- Palmitoylethanolamide + luteolin may not improve olfactory symptoms, RR 1.11 (95% CI 0.68 to 1.81); RD 4.1% (95% CI –11.7% to 29.7%); Low certainty ⊕⊕◯◯

PCC-related cardiovascular system symptoms

The effects of the assessed interventions are uncertain.

PCC-related psychological distress

Virtual reality-based interventions

See Summary of findings Table A14, Annex 1

We identified one RCT including 89 patients in which a virtual reality-based (VR) intervention was compared with standard of care. Our results showed:

- VR may improve depression, RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯
- VR may improve post-traumatic stress, RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯
- VR may improve psychological distress, RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯

PCC-related thromboembolic risk

The effects of the assessed interventions are uncertain.

Full description of included studies

Tables 2 to 8, below, list all the identified studies that were included in this systematic review by intervention and PCC-related organ system affected. The treatments are arranged in alphabetical order. Study or author names, publication status, patient populations, interventions, sources of bias, outcomes, effect sizes, and certainty are listed for each study.

Table 2. Description of included studies and interventions effects for PCC-related asthenia or fatigue

1-MNA **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Chudzik et al. *(13)*; Peer reviewed; 2022	Patients with post COVID-19 syndrome (asthenia or fatigue after 30 days of acute COVID-19). 25 assigned to 1-MNA 58 mg a day and 25 assigned to standard of care.	Median age 49.5, male 32%, hypertension 14%, diabetes 2%	Not reported (NR)	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

ADAPT-232 (adaptogens) ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Karosanidze et al. *(14)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.84 to 1.24); RD 1.6% (95% CI –12.6% to 18.9%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Arginine + Vitamin C Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Tosato et al. *(15)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 28 days of acute COVID-19). 23 assigned to Arginine + Vitamin C 1.66 g/500 mg for 28 days and 23 assigned to standard of care.	Mean age 50.5 ± 14, male 34.8%, interval between COVID-19 and enrolment 254 days, hospitalization during COVID-19 56.5%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** No information **Strength improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Coenzyme Q10 (CQ10) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Hansen et al. *(16)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 84 days of acute COVID-19). 59 assigned to coenzyme Q10 500 mg a day for 6 weeks and 60 assigned to standard of care.	Median age 49, male 25.2%, obesity 33.6%, interval between COVID-19 and enrolment 288.55 days, hospitalization during COVID-19 15.1%	NR	Low risk of bias	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Cytoflavin Cytoflavin may not improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
CITADEL trial *(17)*, Putilina et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 30 to 90 days of acute COVID-19). 50 assigned to cytoflavin 2 tablets a day for 25 days and 50 assigned to standard of care.	Mean age 40.4 ± 12, male 57%, hypertension 38%, diabetes 4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 1.02 (95% CI 0.98 to 1.06); RD 2.1% (95% CI –1.9% to 6.2%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Enzymes + probiotics Enzymes + probiotics may improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Rathi et al. *(18)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after acute COVID-19). 100 assigned to enzymes + probiotics ImmunoSEB (500 mg/capsule) + ProbioSEB CSC3 (5 billion CFUs /capsule) and 100 assigned to standard of care.	Mean age 41.2 ± 13, male 63.5%, interval between COVID-19 and enrolment 19.5 days, one comorbidity 14.5%	NR	High risk of bias Notes: Concealment of allocation and blinding probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 6.07 (95% CI 3.79 to 9.71); RD 76% (95% CI 41.8% to 85%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Fermented food supplements Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Kharaeva et al. *(19)*; Peer reviewed; 2022	Patients with post COVID-19 condition after moderate infection (asthenia or fatigue after acute COVID-19). 68 assigned to fermented food supplements 14 g twice a day for 20 days and 29 assigned to standard of care.	Age 38–69, male 51.5%, hypertension 36.1%, diabetes 15.5%, chronic lung disease 14.4%, obesity 19.6%, hospitalization during COVID-19 46.4%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Kharaeva et al. *(19)*; Peer reviewed; 2022	Patients with post COVID-19 condition after severe infection (asthenia or fatigue after 0 days of acute COVID-19). 64 assigned to fermented food supplements 14 g twice a day for 20 days and 27 assigned to standard of care.	Age 36–65, male 47.2%, diabetes 28.6%, chronic lung disease 20.9%, asthma 3.3%, chronic heart disease 37.5%, obesity 40.6%, hospitalization during COVID-19 41.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Hydrogen (nasal) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Botek et al. *(20)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 21 to 35 days of acute COVID-19). 26 assigned to hydrogen (nasal) 300 mL/min for 14 days and 24 assigned to standard of care.	Mean age 40, male 52%, interval between COVID-19 and enrolment 25 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Leronlimab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Gaylis et al. *(21)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 90 days of acute COVID-19). 27 assigned to Leronlimab 700 mg a week for 8 weeks and 26 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** Very low certainty ⨁◯◯◯ **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Physical training Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Nambi et al. *(22)*; Peer reviewed; 2022	Patients with post COVID-19 condition (sarcopenia after acute COVID-19). 36 assigned to aerobic training (high intensity) and 37 assigned to aerobic training (standard intensity).	Mean age 63.5, male 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** Very low certainty ⨁◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** No information **Functional capacity improvement:** No information **Strength improvement:** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Transcranial direct current stimulation (tDCS) tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Oliver-Mas et al. *(23)*; Preprint; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation (tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19 14.9%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Fatigue improvement:** RR 0.95 (95% CI 0.5 to 1.79); RD –2.4% (95% CI –22.8% to 36.4%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Strength improvement:** No information **Adverse events:** RR 0.83 (95% CI 0.26 to 2.73); RD –3.4% (95% CI –15.5% to 36%); Low certainty ⊕⊕◯◯%) **Severe adverse events:** No information

Telerehabilitation Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
King et al. *(24)*; Preprint; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 110 days of acute COVID-19). 11 assigned to telerehabilitation twice weekly for 10 weeks and 10 assigned to standard of care.	Mean age 48.5 ± 13, male 47.6%, interval between COVID-19 and enrolment 366 days, hospitalization during COVID-19 19%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** Very low certainty ⊕◯◯◯ **Overall symptom improvement:** No information **Fatigue improvement:** Very low certainty ⊕◯◯◯ **Functional capacity improvement:** Very low certainty ⊕◯◯◯ **Strength improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 3. Description of included studies and interventions effects for PCC-related dyspnea

ADAPT-232 (adaptogens) ADAPT-232 may not improve fatigue. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Karosanidze et al. *(14)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1. (95% CI 0.94 to 1.06); RD 0% (95% CI –5.4% to 5.6%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information

Endurance training Endurance training may improve HRQL and dyspnea. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
RECOVER trial. *(25)*, Romanet et al.; Preprint; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 90 days of acute COVID-19). 27 assigned to endurance training rehabilitation (ETR) two (1 h) sessions per week for 10 weeks and 33 assigned to standard of care.	Mean age 58.2, male 61.6%, diabetes 36.7%, chronic lung disease 8.3%, chronic heart disease 5%, cancer 5%, interval between COVID-19 and enrolment 173 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** RR 1.48 (95% CI 0.92 to 2.37); RD 21.2% (95% CI –3.4% to 60.6%); Low certainty ⊕⊕◯◯ **Dyspnea improvement:** RR 2.03 (95% CI 0.98 to 4.21); RD 24.4% (95% CI –0.4% to 75.9%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No information

Respiratory training Respiratory training may improve HRQL and dyspnea. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
ENO Breathe trial *(26)*, Philip et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 30 days of acute COVID-19). 58 assigned to ENO Breathe 6-week program and 71 assigned to standard of care.	Mean age 49.5 ± 12, male 17.3%, interval between COVID-19 and enrolment 320 days, hospitalization during COVID-19 17.3%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** RR 1.93 (95% CI 1.30 to 2.86); RD 24.1% (95% CI –7.8% to 48.1%); Low certainty ⊕⊕◯◯ **Dyspnea improvement:** RR 1.33 (95% CI 0.97 to 1.82); RD 12.3% (95% CI –1.1% to 30.5%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** Very low certainty ⊕◯◯◯ **Radiological response:** No information **Adverse events:** No information **Severe adverse events:** No
McNarry et al. *(27)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after acute COVID-19). 37 assigned to inspiratory muscle training 3 sessions a week for 8 weeks and 37 assigned to standard of care.	Mean age 46.6 ± 12, male 12.8%, interval between COVID-19 and enrolment 270 days	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate. Intention-to-treat (ITT) analysis for primary outcome not available.	
Srinivasan et al. *(28)*; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after acute COVID-19). 24 assigned to respiratory training 3 times a day for 6 weeks and 24 assigned to standard of care.	NR	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

High dose steroids High dose steroids may not improve dyspnea and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
COLDSTER trial *(29)*, Dhooria et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after 21 to 49 days of acute COVID-19). 65 assigned to prednisone 40 mg a day descending progressively to 10 mg a day for 6 weeks and 65 assigned to prednisone 10 mg a day for 6 weeks	Mean age 57, male 68%, one comorbidity 73%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Dyspnea improvement:** RR 1 (95% CI 0.87 to 1.15); RD 0% (95% CI –11.1% to 12.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** No information **Pulmonary function improvement:** No information **Radiological response:** Very low certainty ⊕◯◯◯ **Adverse events:** RR 0.92 (95% CI 0.75 to 1.13); RD –6.2% (95% CI –19.3% to 10%); Low certainty ⊕⊕◯◯ **Severe adverse events:** Very low certainty ⊕◯◯◯

Treamid Treamid may improve dyspnea and pulmonary function but may not improve functional capacity. Treamid may increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Bazdyrev et al. *(30)*; Preprint; 2022	Patients with post COVID-19 condition (dyspnea and/or lung radiological abnormalities after acute COVID-19). 29 assigned to treamid 50 mg a day for 28 days and 30 assigned to standard of care.	Mean age 55 ± 11, male 44.1%	NR	Low risk of bias	**HRQL improvement:** No information **Dyspnea improvement:** RR 1.96 (95% CI 0.9 to 4.25); RD 21.7% (95% CI –2.3% to 73.7%); Low certainty ⊕⊕◯◯ **Functional capacity improvement:** RR 1.10 (95% CI 0.64 to 1.90); RD 4.3% (95% CI –16.2% to 39.8%); Low certainty ⊕⊕◯◯ **Pulmonary function improvement:** RR 2.48 (95% CI 1 to 6.17); RD 24.7% (95% CI 0% to 86.1%); Low certainty ⊕⊕◯◯ **Radiological response:** Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.19 (95% CI

					0.56 to 2.50); RD – 5.5% (95% CI – 12.7% to 43.6%); Low certainty ⊕⊕◯◯ **Severe adverse events:** No information

Table 4. Description of included studies and interventions effects for PCC neurocognitive symptoms

Hyperbaric oxygen (HBO) HBO may improve HRQL. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Zilberman-Itskovich et al. *(31)*; Peer reviewed; 2022	Patients with post COVID-19 condition (neurocognitive symptoms after 90 days of acute COVID-19). 37 assigned to HBO 1 session a day for 40 days and 36 assigned to standard of care.	Mean age 48, male 39.7%, hypertension 8.2%, diabetes 2.7%, chronic lung disease 0%, asthma 4.1%, cancer 0%, obesity 27.4%, interval between COVID-19 and enrolment 165 days, hospitalization during COVID-19 16.4%	NR	Low risk of bias	**HRQL improvement:** RR 1.30 (95% CI 0.84 to 2); RD 13.9% (95% CI –7.4% to 46.9%); Low certainty ⊕⊕◯◯ **Overall symptom improvement:** No information **Cognitive improvement:** Very low certainty ⊕◯◯◯ **Depression improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Transcutaneous auricular vagus nerve stimulation (taVNS) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Badran et al. *(32)*; Preprint; 2022	Patients with post COVID-19 condition (neurocognitive symptoms after acute COVID-19). 6 assigned to transcutaneous auricular vagus nerve stimulation (taVNS) 2 (1 h) sessions a day for 4 weeks and 6 assigned to standard of care.	Mean age 48.5 ± 11.3, male 33.3%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** No information **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Transcranial direct current stimulation (tDCS) tDCS may not improve fatigue and may not increase adverse events. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Oliver-Mas et al. *(23)*; Preprint; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 180 days of acute COVID-19). 23 assigned to transcranial direct current stimulation (tDCS) 1 session a week for 8 weeks and 24 assigned to standard of care.	Mean age 45.6, male 21.3%, hypertension 12.8%, diabetes 4.3%, interval between COVID-19 and enrolment 620 days, hospitalization during COVID-19 14.9%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Cognitive improvement:** RR 0.59 (95% CI 0.33 to 1.05); RD –27.5% (95% CI –44.8% to 3.4%); Low certainty ⊕⊕◯◯ **Depression improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 5. Description of included studies and interventions effects for PCC olfactory and/or gustatory dysfunction

ADAPT-232 (adaptogens) ADAPT-232 may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Karosanidze et al. *(14)*; Peer reviewed; 2022	Patients with post COVID-19 condition (asthenia or fatigue after 30 days of acute COVID-19). 49 assigned to ADAPT-232 (adaptogens) 60 mL a day for 14 days and 50 assigned to standard of care.	Mean age 48.9, male 14%	NR	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 0.89 (95% CI 0.79 to 1.01); RD –10.3% (95% CI –20.5% to 1.4%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Olfactory training Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Di Stadio et al. *(33)*; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 76 assigned to olfactory training and 88 assigned to standard of care.	Mean age 40.7, male 27.6%, hypertension 1.7%, diabetes 0%, chronic heart disease 5.2%	Steroids 44%, vitamins 20.7%, alpha lipoic/nicetile 26.7%	High risk of bias Notes: Non-blinded study which might have introduced bias.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⊕◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information
Pires et al. *(34)*; Preprint; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 26 assigned to advanced olfactory training with 8 essential oils: rose, eucalyptus, clove and lemon, citronella, mint, vanilla and cedarwood and 54 assigned to standard of care.	Mean age 37.6, male 35%	Steroids (nasal) 23.8%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVANOS trial *(35)*, Lechner et al; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 30 days of acute COVID-19). 25 assigned to	Mean age 44, male 13.8%, hypertension 8.9%, diabetes 1.1%, chronic lung disease 0%, asthma 12.6%, chronic heart disease 0%, cancer 2.1%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias.	

	olfactory training for 12 weeks and 26 assigned to standard of care.				

Palmitoylethanolamide + Luteolin

Palmitoylethanolamide + Luteolin may not improve olfactory symptoms. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
RCT					
Di Stadio et al. *(33)*; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after 180 days of acute COVID-19). 88 assigned to palmitoylethanolamide + luteolin 700/70 mg a day and 38 assigned to standard of care.	Mean age 42.1, male 24.6%, hypertension 1.8%, diabetes 0%, chronic heart disease 3.6%	Steroids 32.5%, vitamins 15.8%, alpha lipoic/nicetile 14.9%	Low risk of bias	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** RR 1.11 (95% CI 0.68 to 1.81); RD 4.1% (95% CI –11.7% to 29.7%); Low certainty ⊕⊕◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Steroids (nasal) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
RC 4-7-2020 trial *(36)*, Abdelalim et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after acute COVID-19). 50 assigned to Mometasone 2 puffs (100 µg) once daily in each nostril for 3 weeks and 50 assigned to standard of care.	Mean age 29, male 46%, hypertension 14%, diabetes 16%, hospitalization during COVID-19 31%	Steroids 13%	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⨁◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Steroids Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					

Vaira et al. *(37)*; Peer reviewed; 2022	Patients with post COVID-19 condition (olfactory and/or gustatory dysfunction after acute COVID-19). 9 assigned to prednisone 1 mg/kg a day and 9 assigned to standard of care.	Mean age 42.1, male 38.8%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Olfactory symptoms improvement:** Very low certainty ⨁◯◯◯ **Gustatory symptoms improvement:** No information **Adverse events:** No information **Severe adverse events:** No information

Table 6. Description of included studies and interventions effects for PCC cardiovascular system symptoms

Ivabradine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Jadhav et al. *(38)*; Peer reviewed; 2022	Patients with post COVID-19 condition (cardiovascular symptoms after 0 to 14 days of acute COVID-19). 25 assigned to Ivabradine 5 to 10 mg and 25 assigned to standard of care.	Mean age 48.8 ± 7.66	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Overall symptom improvement:** No information **Tachycardia improvement:** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Severe adverse events:** No information

Table 7. Description of included studies and interventions effects for PCC psychological distress

Virtual reality-based interventions Virtual reality-based interventions may improve depression, post-traumatic stress, and psychological distress. However, certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
ICU-VR trial *(39)*, Vlake et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (psychological distress after 90 days of acute COVID-19). 45 assigned to Virtual reality 14-minute session once and 44 assigned to standard of care.	Mean age 60, male 36%	NR	High risk of bias Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**HRQL improvement:** No information **Depression improvement:** RR 1.21 (95% CI 0.95 to 1.54); RD 14% (95% CI –3.7% to 36.7%); Low certainty ⊕⊕◯◯ **Post-traumatic stress improvement:** RR 1.18 (95% CI 0.98 to 1.42); RD 13.8% (95% CI –1.5% to 32.3%); Low certainty ⊕⊕◯◯ **Psychological distress improvement:** RR 1.49 (95% CI 1.08 to 2.05); RD 25.5% (95% CI 4.1% to 55.1%); Low certainty ⊕⊕◯◯ **Adverse events:** No information

					Severe adverse events: No information

Table 8. Description of included studies and interventions effects for PCC-related thromboembolic risk

Anticoagulants (prophylactic dose) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
MICHELLE trial *(40)*, Ramacciotti et al.; Peer reviewed; 2022	Patients with post COVID-19 condition (at increased risk of VTE after acute COVID-19). 159 assigned to rivaroxaban 10 mg a day for 35 days and 159 assigned to standard of care.	Mean age 57.1, male 60%, interval between COVID-19 and enrolment 8 days, hospitalization during COVID-19 100%	NR	High risk of bias Notes: Non-blinded study which might have introduced bias to symptoms, VTE and adverse events outcomes.	**Mortality:** Very low certainty ⨁◯◯◯ **HRQL improvement:** No information **VTE (symptomatic):** Very low certainty ⨁◯◯◯ **Major bleeding:** No information **Severe adverse events:** No information

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Annex 1. Summary of findings tables

Summary of findings Table A1.

Population: Patients with PCC-related asthenia or fatigue
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ADAPT-232	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement	Relative risk 1.02 (95% CI 0.84 to 1.24) Based on data from 99 participants in 1 study Follow-up 21 days	**800** per 1000	**816** per 1000 Difference: **16 more per 1000** (95% CI 128 fewer to 192 more)	**Low** Due to very serious imprecision[a]	Adapt-232 may have little or no difference on fatigue improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A2.

Population: Patients with PCC-related asthenia or fatigue
Intervention: Cytoflavin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Cytoflavin	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Fatigue improvement[a]	Relative risk 1.02 (95% CI 0.98 to 1.06) Based on data from 200 participants in 1 study Follow-up 25 days	**979** per 1000	**999** per 1000 Difference: **20 more per 1000** (95% CI 20 fewer to 21 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Cytoflavin may have little or no difference on fatigue improvement

a. Decrease in 12 units of the MFI score.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A3.

Population: Patients with PCC-related asthenia or fatigue
Intervention: Enzymes + probiotics
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Enzymes + probiotics		
Fatigue improvement	Relative risk 6.07 (95% CI 3.71 to 9.71) Based on data from 200 participants in 1 study Follow-up 25 days	**150** per 1000	**911** per 1000 Difference: **761 more per 1000** (95% CI 407 more to 850 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Enzymes + probiotics may increase fatigue improvement

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A4.

Population: Patients with PCC-related asthenia or fatigue
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Transcranial direct current stimulation (tDCS)		
Fatigue improvement	Relative risk 0.95 (95% CI 0.5 to 1.79) Based on data from 47 participants in 1 study Follow-up 25 days	**458** per 1000	**435** per 1000 Difference: **23 fewer per 1000** (95% CI 229 fewer to 362 more)	**Low** Due to very serious imprecision[a]	Transcranial direct current stimulation (tDCS) may have little or no difference on fatigue improvement
Adverse events	Relative risk: 0.83 (95% CI 0.26 to 2.73) Based on data from 47 participants in 1 study Follow-up 30 days	**208** per 1000	**173** per 1000 Difference: **35 fewer per 1000** (95% CI 154 fewer to 360 more)	**Low** Due to very serious imprecision[b]	Transcranial direct current stimulation (tDCS) may have little or no difference on adverse events

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A5.

Population: Patients with PCC-related dyspnea
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Dyspnea improvement	Relative risk 1.0 (95% CI 0.94 to 1.06) Based on data from 99 participants in 1 study Follow-up 21 days	**980** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on dyspnea improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A6.

Population: Patients with PCC-related dyspnea
Intervention: Endurance training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Endurance training		
HRQL improvement[a]	Relative risk 1.48 (95% CI 0.92 to 2.37) Based on data from 60 participants in 1 study Follow-up 21 days	**441** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Endurance training may increase HRQL improvement
Dyspnea improvement[c]	Relative risk 2.03 (95% CI 0.98 to 4.21) Based on data from 60 participants in 1 study Follow-up 21 days	**236** per 1000	**980** per 1000 Difference: **0 fewer per 1000** (95% CI 59 fewer to 20 more)	**Low** Due to serious risk of bias, Due to serious imprecision[d]	Endurance training may increase dyspnea improvement

a. Increment of 7 units in the SF-12 scale.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
c. Increment of 7 units in the SF-12 scale.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.

Summary of findings Table A7.

Population: Patients with PCC-related dyspnea
Intervention: High dose steroids (i.e., prednisone 40 mg a day)
Comparator: Standard dose steroids (i.e., prednisone 10 mg a day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard dose steroids	**Absolute effect estimates** High dose steroids	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Dyspnea improvement	Relative risk 1.0 (95% CI 0.87 to 1.15) Based on data from 130 participants in 1 study Follow-up 42 days	**862** per 1000	**862** per 1000 Difference: **0 fewer per 1000** (95% CI 112 fewer to 129 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	High dose steroids may have little or no difference on dyspnea improvement
Radiological response	Relative risk 1.33 (95% CI 0.69 to 2.59) Based on data from 60 participants in 1 study Follow-up 21 days	**185** per 1000	**246** per 1000 Difference: **61 more per 1000** (95% CI 57 fewer to 294 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[b]	We are uncertain whether high dose steroids increases or decreases radiological response
Adverse events	Relative risk 0.92 (95% CI 0.75 to 1.13) Based on data from 60 participants in 1 study Follow-up 21 days	**769** per 1000	**707** per 1000 Difference: **62 fewer per 1000** (95% CI 192 fewer to 100 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	High dose steroids may have little or no difference on adverse events
Severe adverse events	Relative risk 3.0 (95% CI 0.32 to 28.09) Based on data from 60 participants in 1 study Follow-up 21 days	**15** per 1000	**45** per 1000 Difference: **30 more per 1000** (95% CI 10 fewer to 406 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[d]	We are uncertain whether high dose steroids increases or decreases severe adverse events

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
d. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A8.

Population: Patients with PCC-related dyspnea
Intervention: Respiratory training
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Respiratory training	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk 1.93 (95% CI 1.3 to 2.86) Based on data from 203 participants in 2 studies Follow-up 118 days	**259** per 1000	**500** per 1000 Difference: **241 more per 1000** (95% CI 78 more to 482 more)	**Low** Due to serious imprecision, Due to serious risk of bias[a]	Respiratory training may increase HRQL improvement
Dyspnea improvement	Relative risk 1.33 (95% CI 0.97 to 1.82) Based on data from 203 participants in 2 studies Follow-up 118 days	**371** per 1000	**493** per 1000 Difference: **122 more per 1000** (95% CI 11 fewer to 304 more)	**Low** Due to serious imprecision, Due to serious risk of bias[b]	Respiratory training may increase dyspnea improvement
Pulmonary function improvement	Relative risk 1.17 (95% CI 0.66 to 2.07) Based on data from 48 participants in 1 study Follow-up 42 days	**459** per 1000	**537** per 1000 Difference: **78 more per 1000** (95% CI 156 fewer to 491 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[c]	We are uncertain whether respiratory training increases or decreases pulmonary function improvement

a. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: serious.** Low number of patients.
c. **Risk of bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A9.

Population: Patients with PCC-related dyspnea
Intervention: Treamid
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Treamid	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Functional capacity improvement	Relative risk 1.1 (95% CI 0.64 to 1.9) Based on data from 59 participants in 1 study Follow-up 28 days	**445** per 1000	**490** per 1000 Difference: **45 more per 1000** (95% CI 160 fewer to 401 more)	**Low** Due to very serious imprecision[a]	Treamid may have little or no difference on functional capacity improvement
Dyspnea improvement	Relative risk 1.96 (95% CI 0.9 to 4.25) Based on data from 59 participants in 1 study Follow-up 28 days	**227** per 1000	**445** per 1000 Difference: **218 more per 1000** (95% CI 23 fewer to 738 more)	**Low** Due to very serious imprecision[b]	Treamid may increase dyspnea improvement
Pulmonary function improvement	Relative risk 2.48 (95% CI 1.0 to 6.17) Based on data from 59 participants in 1 study Follow-up 28 days	**167** per 1000	**414** per 1000 Difference: **247 more per 1000** (95% CI 0 fewer to 863 more)	**Low** Due to very serious imprecision[c]	Treamid may increase pulmonary function improvement
Adverse events	Relative risk 1.19 (95% CI 0.56 to 2.5) Based on data from 59 participants in 1 study Follow-up 28 days	**290** per 1000	**345** per 1000 Difference: **55 more per 1000** (95% CI 128 fewer to 435 more)	**Low** Due to very serious imprecision[d]	Treamid may increase adverse events

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Imprecision: very serious.** 95% CI includes important benefits and harms.
c. **Imprecision: very serious.** 95% CI includes important benefits and harms.
d. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A10.

Population: Patients with PCC-related neurocognitive symptoms
Intervention: Hyperbaric oxygen (HBO)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HBO	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
HRQL improvement	Relative risk 1.3 (95% CI 0.84 to 2.0) Based on data from 73 participants in 1 study	**469** per 1000	**610** per 1000 Difference: **141 more per 1000** (95% CI 75 fewer to 469 more)	**Low** Due to very serious imprecision[a]	HBO may increase HRQF improvement
Cognitive improvement	Odds ratio 2.84 (95% CI 1.09 to 7.37) Based on data from 73 participants in 1 study	**667** per 1000	**850** per 1000 Difference: **183 more per 1000** (95% CI 19 more to 22 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[b]	We are uncertain whether HBO increases or decreases cognitive improvement
Depression improvement	Odds ratio 35.9 (95% CI 2.72 to 474.6) Based on data from 73 participants in 1 study Follow-up 28 days	**681** per 1000	**987** per 1000 Difference: **306 more per 1000** (95% CI 172 more to 312 more)	**Very low** Due to extremely serious imprecision, Due to serious indirectness[c]	We are uncertain whether HBO increases or decreases depression improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.
b. **Indirectness: serious.** Non appropriately established minimal important difference (MID). **Imprecision: extremely serious.** 95% CI includes important benefits and harms.
c. **Indirectness: serious.** Non appropriately established MID. **Imprecision: extremely serious.** 95% CI includes important benefits and harms.

Summary of findings Table A11.

Population: Patients with PCC-related neurocognitive symptoms
Intervention: Transcranial direct current stimulation (tDCS)
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Transcranial direct current stimulation (tDCS)	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Cognitive improvement	Relative risk 0.59 (95% CI 0.33 to 1.05) Based on data from 47 participants in 1 study Follow-up 30 days	**667** per 1000	**394** per 1000 Difference: **273 fewer per 1000** (95% CI 447 fewer to 33 more)	**Low** Due to very serious imprecision[a]	tDCS may have little or no difference on cognitive improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A12.

Population: Patients with PCC-related olfactory and/or gustatory dysfunction
Intervention: ADAPT-232
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	ADAPT-232		
Olfactory symptoms improvement	Relative risk 0.89 (95% CI 0.79 to 1.01) Based on data from 99 participants in 1 study Follow-up 21 days	**960** per 1000	**854** per 1000 Difference: **106 fewer per 1000** (95% CI 202 fewer to 10 more)	**Low** Due to very serious imprecision[a]	ADAPT-232 may have little or no difference on olfactory symptoms

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A13.

Population: Patients with PCC-related olfactory and/or gustatory dysfunction
Intervention: Palmitoylethanolamide + Luteolin
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		SOC	Palmitoylethanolamide + Luteolin		
Olfactory symptoms improvement	Relative risk 1.11 (95% CI 0.68 to 1.81) Based on data from 126 participants in 1 study Follow-up 90 days	**368** per 1000	**408** per 1000 Difference: **40 more per 1000** (95% CI 118 fewer to 298 more)	**Low** Due to very serious imprecision[a]	Palmitoylethanolamide + luteolin may have little or no difference on olfactory symptoms improvement

a. **Imprecision: very serious.** 95% CI includes important benefits and harms.

Summary of findings Table A14.

Population: Patients with PCC-related psychological distress
Intervention: Virtual reality-based interventions
Comparator: Standard of care (SOC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Virtual reality-based interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Depression improvement	Relative risk 1.21 (95% CI 0.95 to 1.54) Based on data from 89 participants in 1 study Follow-up 90 days	**682** per 1000	**825** per 1000 Difference: **143 more per 1000** (95% CI 34 fewer to 368 more)	**Low** Due to serious risk of bias, Due to serious imprecision[a]	Virtual reality-based interventions may increase depression improvement
Post-traumatic stress disorder improvement	Relative risk 1.18 (95% CI 0.98 to 1.42) Based on data from 89 participants in 1 study Follow-up 90 days	**773** per 1000	**912** per 1000 Difference: **139 more per 1000** (95% CI 15 fewer to 227 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Virtual reality-based interventions may increase post-traumatic stress disorder improvement
Psychologic distress improvement	Relative risk 1.49 (95% CI 1.08 to 2.05) Based on data from 89 participants in 1 study Follow-up 90 days	**523** per 1000	**779** per 1000 Difference: **256 more per 1000** (95% CI 42 more to 549 more)	**Low** Due to serious risk of bias, Due to serious imprecision[c]	Virtual reality-based interventions may increase psychological distress improvement

a. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
b. **Risk of bias: serious. Imprecision: serious.** Low number of patients.
c. **Risk of bias: serious. Imprecision: serious.** Low number of patients.

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