

## An Update of Cardiopulmonary Rehabilitative Measures in Long-COVID-19 Patients: A Systematic Review

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### Abstract

**Background:** The long-term effects of COVID-19 on patients have become an emergent concern. This systematic review aims to evaluate the effectiveness of various post-acute care interventions for COVID-19 patients.

**Methods:** A comprehensive literature search ~~was conducted in accordance with~~ followed PRISMA guidelines across three databases: PubMed, Scopus, and Web of Science. ~~The studies were~~ Two reviewers independently evaluated ~~by two reviewers~~ the studies based on their relevance to the research question, which pertains to the effectiveness of interventions such as home-based pulmonary rehabilitation, inspiratory muscle training, pharmacological treatments, and novel technological methods.

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**Results:** Our review included seven studies, each demonstrating improvement in physical and respiratory function, as well as in quality of life, following diverse interventions. Home-based pulmonary rehabilitation, with and without ~~telecoaching, appeared to improve~~ tele coaching, improved functional outcomes and ~~decreased~~ decreased dyspnea and fatigue. Pharmacological interventions, such as Treamid, showed promise, particularly in women. EMG-driven rehabilitation robots demonstrated feasibility and safety, while H2 inhalation may also be ~~a viable approach~~.

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**Conclusion:** Post-acute care interventions, tailored to individual patient needs, can potentially improve health outcomes in COVID-19 patients. However, the heterogeneity of the included studies necessitates further large-scale randomized controlled trials to ~~definitively~~ ascertain ~~the~~ these interventions' effectiveness ~~of these interventions~~ definitively.

**Keywords:** COVID-19, Post-Acute Care, Pulmonary Rehabilitation, Inspiratory Muscle Training, Pharmacological Treatment, Telecoaching, H2 Inhalation.

## Introduction

The SARS-CoV-2 virus, responsible for Coronavirus Disease 2019 (COVID-19), has precipitated a global health crisis due to its high transmissibility and significant morbidity and mortality (1). ~~To date, nearly~~ Nearly 768 million confirmed cases and millions of associated fatalities have been reported worldwide (2). ~~In response to this unrelenting pandemic, the~~ The global scientific community has rapidly mobilized to elucidate the ~~disease's~~ disease's transmission, prevention, and treatment strategies in response to this unrelenting pandemic. However, as the pandemic's trajectory unfolds, a pressing need has emerged to address the long-term sequelae of COVID-19 and effective post-acute care strategies (3).

Accruing evidence suggests that a significant subset of COVID-19 survivors, colloquially known as ~~long~~ long haulers,' continue to endure persistent symptoms following the acute phase of the infection (4). The observed post-acute COVID-19 symptoms span multiple organ systems—including respiratory, cardiovascular, and neurological—and manifest in various forms, such as dyspnea, fatigue, cognitive impairment, and diminished exercise capacity (5). Furthermore, patients who experienced severe COVID-19 often report functional and mental health deterioration, adversely impacting their quality of life (6,7). These findings highlight the criticality of efficacious post-acute care interventions in mitigating COVID-19's long-term impacts and facilitating patient recovery.

Pulmonary rehabilitation, a recognized intervention for chronic respiratory diseases, may hold promise for enhancing lung function and exercise capacity in COVID-19 survivors, given the virus's primary respiratory system involvement (8). Home-based pulmonary rehabilitation, telecoaching, and inpatient pulmonary rehabilitation are some ~~of the~~ of the modalities being explored for managing post-COVID-19 sequelae (9).

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Simultaneously, pharmacological interventions such as Treamid have been demonstrated to potentially improve lung function in post-COVID patients exhibiting lung fibrosis (10). Non-pharmacological interventions, including inspiratory muscle training and molecular hydrogen inhalation, have also been investigated for their putative benefits in post-acute COVID-19 care (11,12).

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In parallel, technologies, such as EMG-driven rehabilitation robots, have been deployed to counter post-viral fatigue syndrome—a common debilitating symptom in COVID-19 survivors (13). ~~Additionally, respiratory~~ Respiratory rehabilitation training has also been proposed to ~~ameliorate~~ facilitate respiratory function, enhance quality of life, and assuage anxiety in elderly COVID-19 patients (14,15).

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Given the array of interventions under investigation, ~~there is an~~ urgent ~~requirement~~ need is to comprehensively understand their effectiveness in managing post-acute COVID-19 scenarios. This systematic review aims to bridge this knowledge gap by compiling and critically appraising the ~~existing~~ literature on various post-acute care interventions for COVID-19 patients. By systematically evaluating the most recent literature, this review seeks to provide a thorough understanding of these interventions' efficacy, thereby guiding healthcare providers in informed decision-making regarding post-acute COVID-19 care management. Furthermore, the outcomes of this review will lay a robust groundwork for future research endeavors in this crucial healthcare domain.

## Methods

We adhered to PRISMA Statement 2020 guidelines (16). The primary objective of this review is to conduct a comprehensive evaluation of the recent literature assessing the efficacy of various interventions in managing post-COVID complications. The research question is: What are the most effective interventions ~~in the management of~~ for post-COVID complications?

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## PICO Framework

The PICO framework for this systematic review is as follows:

- Population: Patients with post-COVID complications
- Intervention: Various interventions for post-COVID care, including pharmacological treatments, rehabilitation programs, and novel therapies
- Comparison: Standard care or other treatments for post-COVID complications, control groups receiving placebo or no intervention
- Outcome: Changes in clinical, functional, and quality of life measures, complications, side effects, and other relevant health outcomes post-intervention

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### Search Strategy

The systematic literature search focused on studies published between 2020 and 2023 to include the most recent and relevant research findings. This search was executed across three databases: PubMed, Scopus, and Web of Science, to locate pertinent studies. Keywords and MeSH terms such as 'Post-COVID Complications', 'COVID-19', 'Long COVID', 'Intervention', 'Treatment', 'COVID', 'Intervention', 'Treatment', 'Clinical Trial', 'Efficacy', 'Safety', 'Trial', 'Efficacy', 'Safety', among others, and their combinations were used for the search. No restrictions were applied based on language or geographical location, and only peer-reviewed articles were considered eligible for inclusion.

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### Study Selection

The articles retrieved from the initial search were independently evaluated by two reviewers based on their titles and abstracts to determine their relevance to the topic of post-COVID complications and various interventions in their management. Any reviewer disagreements between the reviewers were resolved through discussion or by consulting a third reviewer if necessary. The full texts of the shortlisted articles were procured for further in-depth review. Studies were included if they met the following criteria: original research studies published between 2020

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and 2023, studies focusing on the role of various interventions in managing post-COVID complications, and studies that provided adequate data for extraction and analysis.

### Data Extraction and Synthesis

~~Data~~ ~~The research team systematically extracted data~~ from the included studies ~~were systematically extracted by the research team~~. The data extracted included the following details: author names, year of publication, study design, intervention, population characteristics, ~~main~~ primary results, and clinical implications. The extracted data were then synthesized and analyzed qualitatively. The ~~primary~~ preliminary findings were compiled and summarized. This provided an overview of the current state of interventions in managing post-COVID complications.

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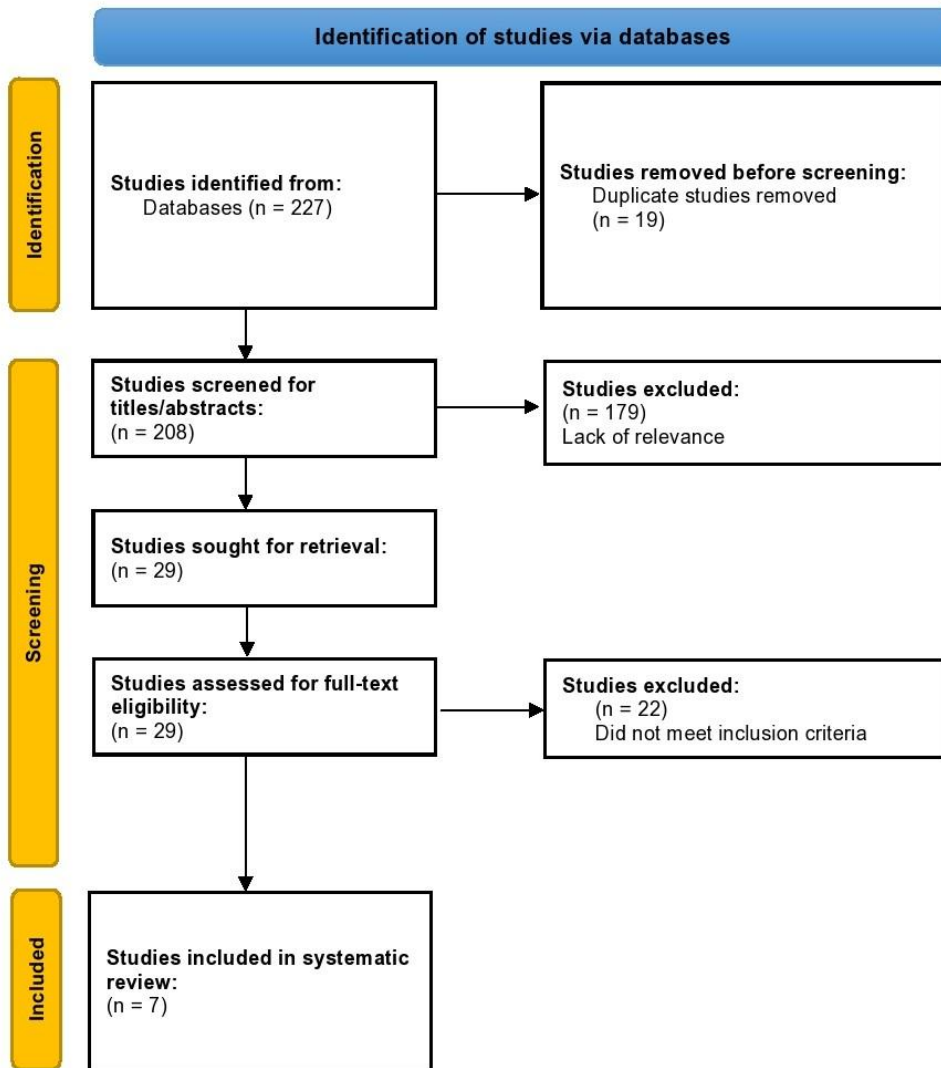
### Results

Of the 227 studies identified, 19 were removed before screening. In the screening phase, 208 were screened for titles and abstracts. Of these, 179 were excluded for lack of relevance. In total, 29 studies were assessed for full-text eligibility, of which ~~7~~ seven were included in the systematic review.

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**Figure 1.** PRISMA flowchart depicting the study selection process.

The characteristics of the included studies are tabulated and presented in **Table 1**.

**Table 1.** Characteristics of all the included studies.

Author, Year	Title	Study Design	Intervention	Population Characteristics	Main Results	Implications for Post-COVID-Care
Şahin, 2023	Effects of a home-based pulmonary rehabilitation program with and without telecoaching on health-related outcomes in COVID-19 survivors: a	Randomized control trial	Home-based pulmonary rehabilitation (PR) program with and without telecoaching	42 COVID-19 patients who completed medical treatment	-Both groups improved FVC, six-minute walk distance, right and left deltoid muscle strength, Saint George's	Home-based PR with telecoaching can lead to improved social functioning and decreased dyspnea and fatigue in post-COVID

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		randomized controlled clinical study				Respiratory Questionnaire activity and impact domain scores, and SF-36 scores (P< 0.05) -Decreases in daily-life dyspnea, exertional dyspnea, and exertional fatigue were significant in the study group (P< 0.05) -The improvement in SF-36 social functioning domain scores was	patients.
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						greater <b>more significant</b> in the study group (P<0.05)	
Vallier, 2023	Randomized controlled trial of home-based vs. hospital-based pulmonary rehabilitation in post-COVID-19 patients	Randomized control trial	Comparison of inpatient pulmonary rehabilitation (IPR) and home-based pulmonary rehabilitation (HPR)	17 post-COVID-19 patients randomized into two groups for IPR or HPR	Both groups improved 6MWT distance (IPR +95 m vs. HPR +72 m, P<0.001), with no significant interaction between time and group (P=0.420)	Home-based pulmonary rehabilitation could be as effective as inpatient rehabilitation in alleviating physical sequelae in post-COVID-19 patients	
Bazdyrev, 2022	Efficacy and safety of Treamid in the rehabilitation of patients after COVID-19 pneumonia: a	Phase 2, randomized, double-blind, placebo-controlled clinical trial	Comparison of Treamid 50 mg or placebo peroral administration for 4 weeks	Post-COVID patients with lung fibrosis and decreased lung function were randomized	-The Treamid group (41%), compared to the placebo group (17%), showed significantly	Treamid might be a promising pharmacological treatment for long-term sequelae in post-COVID	

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		phase 2, randomized, double-blind, placebo-controlled trial			into two groups to receive Treamid or a placebo	improved FVC and DLCO (P=0.036) -The modified Borg scale showed a significant reduction in dyspnea in the Treamid group (- 0.9 0.7 vs. - 0.4 0.8, P=0.018) -Exploratory analysis showed superior improvement in the female population in the Treamid group	patients, particularly in women. This finding supports further investigation in future clinical trials.
Botek,	Molecular Hydrogen	Randomized, single-	Inhalation of molecular	Acute post-COVID-19	In comparison to	H2 inhalation may be a safe,	

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2022	Positively Affects Physical and Respiratory Function in Acute Post-COVID-19 Patients: A New Perspective in Rehabilitation	<del>blinded</del> masked, placebo-controlled study	hydrogen (H2) for 14 days, twice for a total of one hour each per day	patients (26 males, 24 females) were randomized into two groups, one receiving H2 and the other receiving a placebo	placebo, H2 therapy increased 6MWT distance by $64 \pm 39$ m, FVC by $0.19 \pm 0.24$ L, and FEV1 by $0.11 \pm 0.28$ L (all $P \leq 0.025$ )	effective approach for improving physical and respiratory function in acute post-COVID-19 patients
Palau, 2022	Effect of a home-based inspiratory muscle training programme on functional capacity in postdischarged patients with long COVID: the InsCOVID trial	Single-center, blinded assessor, randomized controlled trial	Home-based inspiratory muscle training (IMT) programme	26 patients with long COVID and a previous admission due to SARS-CoV-2 pneumonia were randomly assigned to receive either a 12-week IMT or usual care alone	-The IMT group significantly improved their peak oxygen consumption (peak VO2) compared with the usual care group ( $P < 0.001$ ) -Positive findings were also observed	IMT improved exercise capacity and quality of life in long-term COVID patients with SARS-CoV-2 pneumonia

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						in the chronotropic index and some quality-of-life dimensions	
Zasadzka, 2022	Application of an EMG-Rehabilitation Robot in Patients with Post-Coronavirus Fatigue Syndrome (COVID-19)-A Feasibility Study	Pilot study	EMG-driven rehabilitation robot	Patients with Post-Viral Fatigue (PVF) syndrome after COVID-19 were randomly assigned to two groups, one with and one without the intervention	-Both groups improved in most measured parameters except for muscle fatigue -Muscle fatigue scores presented non-significant improvement in the intervention group and non-significant deterioration	Using an EMG rehabilitation robot in patients with PVF can be feasible and safe; more evidence is required to corroborate the findings.	

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						in the control group	
Liu, 2020	Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study	Observational, prospective, quasi-experimental study	Six-week respiratory rehabilitation training	72 elderly patients with COVID-19, with 36 of them undergoing respiratory rehabilitation and the rest receiving no intervention	-The intervention group showed significant improvements in FEV1(L), FVC(L), FEV1/FVC%, DLCO%, and 6-min walk test -SF-36 scores, in 8 dimensions, and SAS anxiety scores were statistically significant within the intervention group and between the two groups		Six-week respiratory rehabilitation improves elderly COVID-19 patients' respiratory function, quality of life, and anxiety, but not depression

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						-SDS depression scores showed <del>the slight</del> significant improvement	
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**Abbreviations:** 6MWT stands for Six-minute walk test; COVID-19 is an abbreviation for Coronavirus Disease 2019; DLCO represents Diffusing Capacity of the Lung for Carbon Monoxide; EMG is short for Electromyography; FEV1 refers to Forced Expiratory Volume in 1 second; FVC stands for Forced Vital Capacity; H<sub>2</sub> is an abbreviation for Molecular Hydrogen; HPR represents Home-based Pulmonary Rehabilitation; IMT is an abbreviation for Inspiratory Muscle Training; IPR stands for Inpatient Pulmonary Rehabilitation; L is short for Liter; M refers to Meter; PR represents Pulmonary Rehabilitation; PVF is an abbreviation for Post-Viral Fatigue; SAS stands for Self-Rating Anxiety Scale; SDS is short for Self-Rating Depression Scale; SF-36 refers to 36-Item Short Form Survey; VO<sub>2</sub> is an abbreviation for Oxygen Consumption.

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The study by Şahin (2023) implemented a randomized control trial design to test a home-based pulmonary rehabilitation (PR) program both with and without telecoaching on 42 post-COVID patients (17). Notably, both intervention groups ~~showed improvements in~~ improved Forced Vital Capacity (FVC), six-minute walk distance, right and left deltoid muscle strength, Saint George's Respiratory Questionnaire activity and impact domain scores, and SF-36 scores. However, the telecoaching group demonstrated more significant improvements in social functioning and decreased daily-life dyspnea, exertional dyspnea, and exertional fatigue. These findings suggest that home-based PR with telecoaching can lead to improved social functioning and ~~decreased~~ reduced dyspnea and fatigue in post-COVID patients.

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Next, a study by Vallier (2023) randomized 17 post-COVID-19 patients into two groups to receive either inpatient pulmonary rehabilitation (IPR) or home-based pulmonary rehabilitation (HPR) (18). Both groups improved the 6-minute walk test (6MWT) distance (IPR +95 m vs. HPR +72 m,  $P < 0.001$ ), with no significant interaction between time and group ( $P = 0.420$ ). These results suggest that home-based pulmonary rehabilitation could be as effective as inpatient rehabilitation in alleviating physical sequelae in post-COVID-19 patients.

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Bazdyrev (2022) conducted a Phase 2, randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of Treamid, a drug given orally for four weeks, on post-COVID patients with lung fibrosis and decreased lung function (19). The Treamid group (41%), compared to the placebo group (17%), showed significantly improved FVC and Diffusion Capacity for Carbon Monoxide (DLCO) ( $P = 0.036$ ). The modified Borg scale showed a significant reduction in dyspnea in the Treamid group, and superior improvement was observed in the female population in the Treamid group. This indicates that Treamid might be a promising pharmacological treatment for long-term sequelae in post-COVID patients, particularly in women, and supports further investigation in future clinical trials.

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In another randomized, single-blind, placebo-controlled study by Botek (2022), acute post-COVID-19 patients were assigned to receive either molecular hydrogen (H<sub>2</sub>) inhalation for 14 days or a placebo (20). Compared to the placebo group, the H<sub>2</sub> therapy group experienced an increased 6MWT distance by  $64 \pm 39$  m, FVC by  $0.19 \pm 0.24$  L, and Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) by  $0.11 \pm 0.28$  L (all  $P \leq 0.025$ ). The study concluded that H<sub>2</sub> inhalation may be a safe, effective, practical approach for improving physical and respiratory function in acute post-COVID-19 patients.

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The study by Palau (2022) applied a single-center, blinded assessor, randomized controlled trial design to test a home-based inspiratory muscle training (IMT) programme on 26 patients with long COVID and a previous admission due to SARS-CoV-2 pneumonia (21). The IMT group significantly improved their peak oxygen consumption (peak VO<sub>2</sub>) compared with the usual care group ( $P < 0.001$ ), and positive findings were also observed

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in the chronotropic index and some quality-of-life dimensions. These findings suggest that IMT improved exercise capacity and quality of life in long-term COVID patients with a previous admission due to SARS-CoV-2 pneumonia.

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An experimental pilot study by Zasadzka (2022) used an EMG-driven rehabilitation robot on patients with Post-Viral Fatigue (PVF) syndrome after COVID-19 (13). While both intervention and control groups improved in most measured parameters, except for muscle fatigue, the intervention group demonstrated non-significant improvements in muscle fatigue scores, while. In contrast, the control group showed non-significant deterioration. Thus, using an EMG rehabilitation robot in patients with PVF can be feasible and safe; however, more evidence is required to corroborate these findings.

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Lastly, an observational, prospective, quasi-experimental study by Liu (2020) applied a six-week respiratory rehabilitation training to 72 elderly COVID-19 patients (22). The intervention group showed significant improvements in FEV1(L), FVC(L), FEV1/FVC%, DLCO%, and 6-min walk test, as well as SF-36 scores in eight dimensions and SAS anxiety scores. These results suggest that six-week respiratory rehabilitation can improve the respiratory function, quality of life, and anxiety of elderly patients with COVID-19. However, the intervention had ~~the~~ a slight significant improvement ~~on~~ in SDS depression scores.

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## Discussion

This systematic review synthesized and critically appraised the most recent literature on post-acute care interventions for COVID-19 patients. The evidence examined encompassed a diverse array of interventions, each contributing uniquely towards a more comprehensive understanding of post-acute COVID-19 care.

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The results indicate that pulmonary rehabilitation programs, both inpatient and home-based, can significantly improve physical and respiratory function in post-acute COVID-19 patients (23). This aligns with the long-established role of pulmonary rehabilitation in managing chronic respiratory conditions (24). Additionally, the role

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~~of telecoaching~~ tele coaching in enhancing the effects of home-based pulmonary rehabilitation programs is notable, especially considering the importance of remote healthcare delivery in the ongoing pandemic scenario (25). However, more high-quality studies are needed to assess ~~the~~ these interventions' long-term effects and ~~the~~ optimal duration ~~of these interventions~~.

Pharmacological interventions, particularly Treamid, ~~exhibited promising results in improving~~ improved lung function in post-acute COVID-19 patients with lung fibrosis (10,19). These findings underscore the potential role of Treamid in managing long-term sequelae in post-COVID patients, particularly in women (19). Given the preliminary nature of these results, future trials are required to ~~further~~ evaluate further the safety and efficacy of Treamid in broader populations and over extended periods (19).

Non-pharmacological interventions like inspiratory muscle training (IMT) and molecular hydrogen inhalation demonstrated promising outcomes, improving exercise capacity and quality of life (26). These findings suggest that such interventions could be incorporated into the comprehensive management of post-acute COVID-19 patients (27). Still, more rigorous, randomized controlled trials are necessary to substantiate these initial findings.

Novel interventions, such as EMG-driven rehabilitation robots, were found to be feasible and safe for patients with post-viral fatigue syndrome after COVID-19, ~~though~~ However, the evidence supporting their effectiveness remains limited (13). This novel approach has the potential to aid in post-COVID-19 rehabilitation, especially considering the technological advancements and the shift ~~towards~~ toward digital health solutions.

Respiratory rehabilitation training in elderly COVID-19 patients ~~appears to have a substantial positive effect~~ substantially positively affects respiratory function, quality of life, and anxiety (22). This aligns with the increasing focus on personalized medicine and the importance of considering patient demographics when formulating intervention strategies. However, the impact of this intervention on depression scores was negligible, highlighting the need for integrated psychosocial support in post-acute COVID-19 care (28).

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While the current review provides ~~important~~essential insights into post-acute care interventions for COVID-19 patients, it is imperative to consider the potential limitations. Heterogeneity across the included studies ~~in terms~~ ~~of~~regarding patient characteristics, intervention protocols, and outcome measurements precludes a direct comparison of results and warrants careful interpretation. Furthermore, the novelty of COVID-19 and the emergent understanding of its long-term effects make it challenging to draw definitive conclusions.

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## Conclusion

This systematic review has ~~provided a comprehensive evaluation of~~comprehensively evaluated the current literature on post-acute care interventions for COVID-19 patients. Our findings indicate that diverse interventions, including pulmonary rehabilitation, inspiratory muscle training, pharmacological treatment, and even novel technological methods, show promising potential in addressing the physical and respiratory sequelae in post-acute COVID-19 patients. Specifically, ~~it appears that a~~ comprehensive, multifaceted approach ~~that is~~ tailored to individual patient needs can significantly improve health outcomes and quality of life.

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However, given the heterogeneity in study designs, patient populations, and outcome measures across the included studies, the findings must be interpreted ~~with caution~~cautiously. As our understanding of COVID-19 and its long-term effects ~~continue~~continues to evolve, ~~it is crucial to conduct~~conducting further high-quality, ~~large scale~~ randomized controlled trials is crucial. This will help to more definitively ascertain ~~the~~these interventions' effectiveness ~~of these interventions~~ and ~~thereby~~ inform future guidelines for post-acute care for COVID-19 patients. In this rapidly evolving field, continued research and systematic reviews of emerging evidence are imperative for optimizing care for post-acute COVID-19 patients.

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