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Review Article

Evaluation of Exercise Rehabilitation Programs to Improve Cardiac and Respiratory Health in COVID-19 Patients: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) survivors have suffered from long-term impacts of the disease. Many survivors are experiencing persistent cardiac and respiratory complications. Some studies have shown that exercise-based rehabilitation plays a critical role in the recovery of post-COVID-19 patients in order to minimize complications such as dyspnea, breathlessness, and heart failure.

Objective: The objective of this study was to evaluate the effectiveness of exercise-based rehabilitation programs to improve cardiac and respiratory functions in COVID-19 patients.

Methodology: An extensive search of literature was conducted on PubMed, Cochrane Central Register of Controlled Trials, and TRIP databases using the following keywords and Boolean operators: High intensity interval training (HIIT) OR rehabilitation OR COVID-19 OR exercise AND long COVID. Randomized controlled trials (RCTs) published in the English language from 2020 to 2024 were included in the study. Full-text articles were reviewed and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines were implemented during this systematic review. Patients who had pre-existing cardiac and respiratory complications were excluded from the study.

Results: This systematic review included 5 RCTs involving 291 participants. The rehabilitation (intervention) groups showed notable improvements in VO_2 peak with pooled data (ES = 0.765, SE = 0.193, 95% confidence interval [CI] 0.391, 1.139). The mean difference (MD) for VO_2 peak was 2.42, maximum, heart rate (HR max) increased (MD = 5.33), and the left ventricular mass increased by MD = 6.8 (95% CI: 0.8; 12.8 g; P = 0.029) indicating enhanced cardiovascular conditioning and function. Maximum voluntary ventilation (MD = 5.3) improved respiratory endurance along with an increased stability in FEV_1 and FVC. In addition, a drastic improvement in the ventilatory efficiency and breathing patterns was noted, thus reducing perceived dyspnea. HIIT intervention: Two participants showed a reduction in their predicted residual volume % (8%) and total lung capacity. In comparison, the control group showed no significant improvement.

Conclusion: Exercise-based rehabilitation programs have shown improvement in cardiac and respiratory functions by decreasing symptoms such as dyspnea, palpitations, and failure. By integrating such rehabilitation programs into post-COVID care, long-term recovery can be significantly improved.

Keywords: Rehabilitation, Exercise therapy, Long COVID, Coronavirus disease 2019, Cardiovascular, Respiratory rehabilitation

INTRODUCTION

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) has a broad spectrum of clinical manifestations and has impacted over 77 million people globally since 2019. Around 66 million deaths were confirmed according to the World Health Organization (WHO) reports.[1] Coronavirus disease 2019 (COVID-19) is considered a multisystem disease as it affects the respiratory, cardiac, vascular, nervous, and renal systems. A study reported that COVID-19 has increased the incidence of heart failure and cardiovascular complications by 11.61 cases and 23.4 cases/1000 people.[2], respectively. Patients who recovered have experienced long-term lung damage such as inflammation and interstitial lung lesions which lead to breathlessness and dyspnea.[3-5] To address such complications, exercise rehabilitation programs such as high-intensity interval training (HIIT), supervised exercise, respiratory muscle training, and endurance training have shown significant improvements in symptoms such as dyspnea, breathlessness, even decreasing the risk of heart failure, and palpitations.[6-10]

Existing literature supports the effectiveness of exercise rehabilitation programs on a single system or whole-body system rather than focusing on these two isolated cardiac and respiratory stems together under one framework. There is a dearth of data regarding the effects of cardiopulmonary rehabilitation programs on both cardiac and respiratory systems in post-COVID-19 survivors. Hence, this systematic review addresses this gap by evaluating the effectiveness of comprehensive exercise rehabilitation programs that improve both the cardiac and respiratory functions together in COVID-19 patients.

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guidelines were followed.

Search strategy

This systematic review considered the impact of rehabilitation programs that were found to improve cardiac and respiratory sequelae in COVID-19. A thorough search of literature was done on the PubMed, Cochrane Central Register of Controlled Trials, and TRIP databases. Medical subject headings terms were used to develop a search strategy (high-intensity interval training) OR (rehabilitation) OR (COVID-19) OR (exercise) AND (long COVID) were combined using the above-mentioned Boolean operators [Table 1].

Table 1: Various databases searched.

Databases searched	Boolean operators and keywords	Total number of articles
PubMed	(high intensity interval training) OR (rehabilitation)) OR (COVID-19)) OR (exercise)) AND (long COVID)) Filters: from 2020 to 2024	35313
Cochrane Central Register of Controlled Trials	(high intensity interval training) OR (rehabilitation)) OR (COVID-19)) OR (exercise)) AND (long COVID) in Title Abstract Keyword Filter: from January 1, 2020 to October 1, 2024	1984
Trip	(high intensity interval training) OR (rehabilitation)) OR (Covid-19)) OR (exercise)) AND (long Covid) from_date: January 01, 2000 to_date: October 1, 2024	2066
		39,363

Inclusion criteria

Randomized controlled trials (RCTs) that were published between 2020 and 2024 were included in this systematic review. Full-text manuscripts available in the English language were included in this study.

Exclusion criteria

Non-RCTs, cohort studies, cross-sectional studies, case–control studies, case series, case studies, or letter to the editor manuscripts were rejected. Patients who had pre-existing cardiovascular and respiratory health conditions and studies with an age group of <18 years old were excluded from the study.

Study selection

Two reviewers (NJ and RS) independently evaluated titles and abstracts and articles that met the requirements, and were selected for full-text review. The full texts were then evaluated, retrieved, and assessed by the same two reviewers.

Data synthesis

Two independent researchers (NJ and KD) extracted the data, which included the authors information, the year of publication, study characteristics, sample size, and the type of article reviewed and findings which indicated improvement in cardiac and respiratory health as well as higher levels of VO_2 max and heart rates in the intervention groups. In case of disagreements, the perspective of a third researcher (SK) was considered.

Quality assessment

The Cochrane risk-of-bias method for randomized trials (RoB 2) was used and the quality assessment was done by two independent researchers (NS and KD) to assess risk

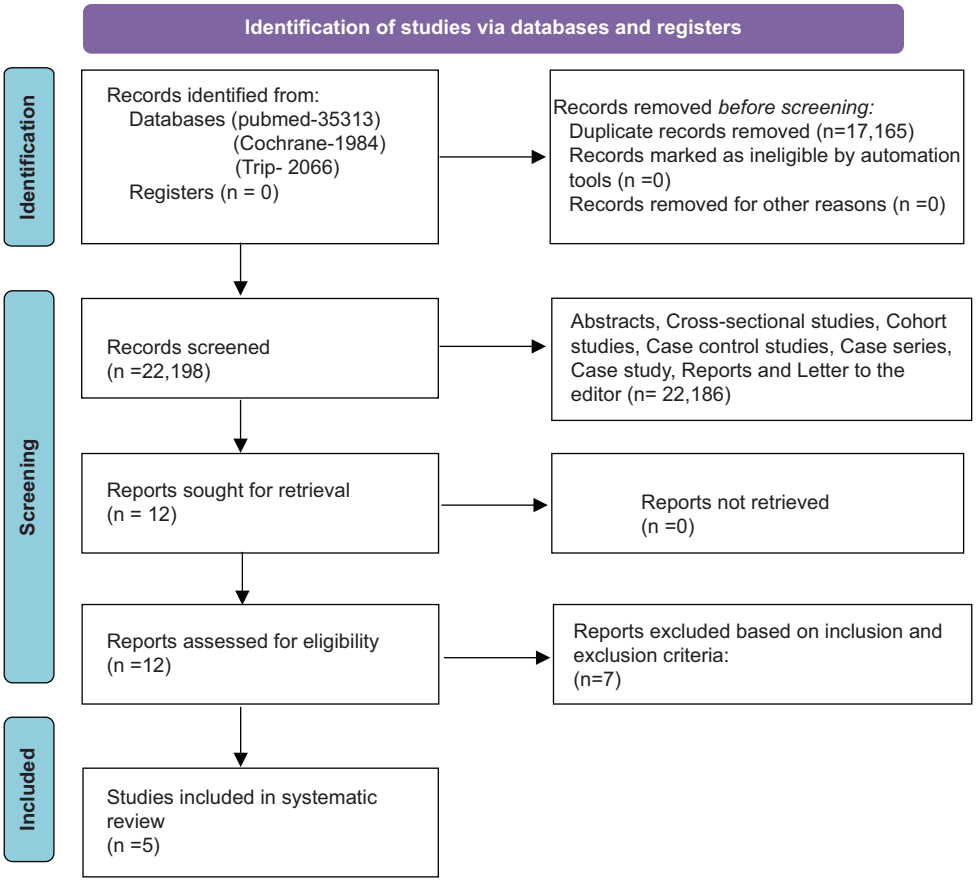

Figure 1: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart outlining the study selection process for the systematic review.

of bias. Five domains were taken into consideration while creating traffic light plots and bar plots: randomization, deviation, missing outcome data, outcome measurement, and reported review selection were considered. All of the studies were rated as either high, no information or low risk of bias. A web-based application program, Robvis visualization tool was used for the visualization of the risk of bias assessment by developing traffic light plots and weighted bar plots for the risk of bias summary and figure.

RESULTS

The systematic review consists of 5 RCTs. The articles identified through an extensive search on three databases generated 39,363 manuscripts. Among these, the duplicate records were removed (n = 17,165). Records screened during the research amounted to 22,198. Records were also excluded due to study design (n = 22,186). Ultimately twelve records were accessed for eligibility criteria and a total of seven records were excluded based on the inclusion and exclusion criteria. Finally, five records were included in the systematic review. The five RCTs involved a total of 291 participants [Figure 1]. These RCTs have shown significant improvements

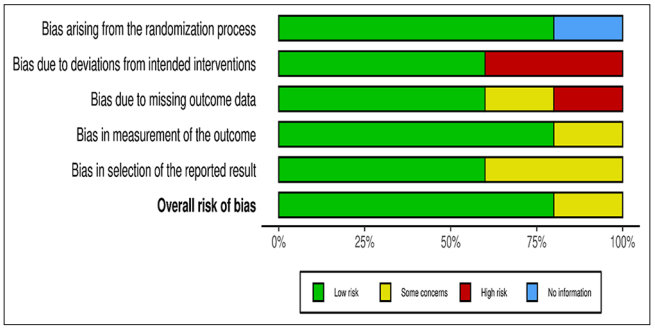

Figure 2: Summary of the risk of bias for randomized controlled trials (weighted bar plot).

in the rehabilitation intervention groups. On the contrary, the control group showed no significant improvement.

Risk of bias assessment

Robvis visualization tool is a web-based application program, designed for the visualization of risk of bias assessment as a part of a systematic review by developing traffic light plots, and weighted bar plots for risk of bias summary and figure [Figures 2 and 3].

Figure 2 shows a weighted bar plot for the risk of bias summary and Figure 3 shows a traffic light plot. The figure of the risk of bias was generated based on five domains. All the included RCTs underwent a quality assessment by the RoB 2 tool. Overall risk of bias for the five RCTs was found to be at a low risk 80% and 20% of the RCTs represented some concerns.

Bias arising from the randomization process (domain 1) 80% of the RCTs were at low risk, for the second domain bias due to deviations from intended interventions, 60% of the RCTs were found to be at low risk, for the third domain bias due to missing outcome data, 60% were at low risk, for the fourth domain bias due to measurement of the outcome, 80% were at low risk, and for domain 5 bias in the selection of reported results, low risk was found in 60% of the RCTs.

Details of studies showing the country of study, study design the number of intervention patients, the number of control group patients, intervention given, major findings, limitations, and outcome of the five RCTs have been depicted in Tables 2 and 3, respectively.

Improvement analysis of VO_2 peak and maximum heart rate (HR max) between the rehabilitation group and control group in each RCTs.

The mean difference (MD) for VO_2 peak was 2.42, the HR max value increased (MD = 5.33), and left ventricular

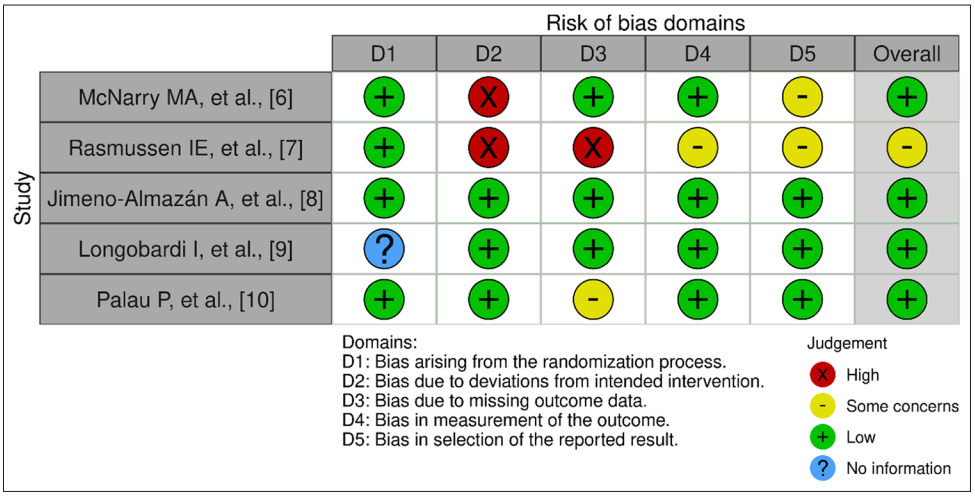

Figure 3: Figure of risk of bias of randomized controlled trials (traffic light plot).

Table 2: Details of studies showing the country of study, study design the number of intervention patients, the number of control group patients, and intervention given.

Author, year	Country	Study design	Intervention group	Control group	Intervention given
Mcnarry *et al.*, 2022[6]	United Kingdom	RCT	111	37	Aerobic Exercise, Respiratory Muscle Training, IMT, Physical Exercise, Strength Exercise.
Rasmussen *et al.*, 2023[7]	Denmark	RCT	14	14	12-week HIIT [High Intensity Interval Training] scheme: 3 training session on A Bicycle Ergometer [Aerobic Training].
Jimeno-Almazán *et al.*, 2022[8]	Spain	RCT	19	20	Multicomponent Exercise Program based on concurrent training for 8 weeks through supervised interventions [Resistance Training combined with Aerobic Training, Moderate Intensity Variable Training], monitored light Intensity continuous training].
Longobardi *et al.*, 2023[9]	Brazil	RCT	25	25	HBET Program: A semi-Supervised Exercise Program conducted 3 times in a week for about 60–80 min per session. Exercise Cards and Videos, Aerobic Training, Strength Training, Active Stretching.
Palau *et al.*, 2022[10]	Spain	RCT	13	13	A Home-Based 12-week Program of IMT arm training using Threshold Inspiratory Muscle Trainer.

RCT: Randomized controlled trials, IMT: Inspiratory muscle training, HBET: Home-based exercise training

Table 3: Details of studies showing major findings, limitations, and outcome.

Author, year	Findings	Limitations	Outcome
Mcnarry *et al*., 2022[6]	VO_2 peak is increased by 5.2 mL/kg/min. Effect size=0.43.	Small sample size with majority of female generalizability developed. Short follow up period.	The participants in the rehabilitation group showed significant improvement in Cardiovascular Fitness and had a higher VO_2 peak than the control group.
Rasmussen *et al*., 2023[7]	At baseline 15% (4/26) patient had LVM values below normal range. After intervention values reduced to LVM 4% I (1/25). HIIT group increased by 6.8 g. This is statistically significant. VO_2 peak increased by 3.1 mL/kg/min. Baseline for DLCOc% prediction reduced in participants (13/26). After intervention the participants are reduced to 5/26.	Lack of data on LVM, lung function, and exercise capacity of the participants before the COVID-19 infection. High withdrawal rate.	The high-intensity interval training (HIIT) has beneficial effect on cardiac function as compared to control group. Improvement in VO_2 peak showed better Cardiorespiratory Health. Improvement in DLCOc% predicted is seen.
Jimeno-Almazán *et al*., 2022[8]	VO_2 peak improved in the exercise group by a mean of 2.1 mL/kg/min (5.9% SD 9.2). Reduction in heart rate Final=13.3% mean difference (MD) =9 BPM	Study population may not represent all post-COVID-19 cases, especially severe ones. Lack of pre-infection exercise data makes it difficult to assess true changes. Mood disorders and pre-existing activity levels may influence exercise program effectiveness.	Improvement In HR Max, PVO_2 values in rehabilitation group in comparison to the control showed better Cardiopulmonary Health.
Longobardi *et al*., 2023[9]	VO_2 peak increased with mean difference=4.46. HRmax MD=11 bpm Chronotropic index MD = (+0.13)	Single-center design. Small sample size. Short follow-up period.	Better maintenance of Cardiovascular Performance. Positive impact on Respiratory Endurance and sufficiency. Increase in chronotropic index in training group suggests an improved heart rate response to exercise.
Palau *et al*., 2022[10]	VO_2 Peak increased by 0.1 mg/kg/min Maximum voluntary ventilation (Maximal ventilator efficiency increased by 18.9%. HRmax MD=−4	Small number of participants. Evaluated patients with long COVID post -hospitalization due to SARS-CoV-2 Pneumonia.	Improvement in pulmonary function compare to control Reduction in dyspnea.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus, DLCO: Diffusing capacity for carbon monoxide, VO_2: Peak oxygen uptake, LVM: Left ventricular mass, HR MAX: Maximum heart rate, HR: Heart rate

mass (LVM) increased by MD = 6.8 indicating enhanced cardiovascular conditioning and functioning. Maximum voluntary ventilation (MD = 5.3) improved respiratory endurance along with increased stability in FEV_1 and FVC.

Therefore, we can deduce that the intervention group demonstrated a significant improvement in respiratory as well as the cardiovascular system functions. On the contrary, the control group showed a lower less or no improvement as per the data [Table 4].

DISCUSSION

This systematic review revealed that the exercise-based rehabilitation programs improved the cardiovascular and respiratory sequelae, such as dyspnea, chest pain, heart failure, pulmonary hypertension, and arrhythmias in post-COVID-19 survivors. This study showed that the effects of HIIT programs on cardiopulmonary health in post COVID-19 patients acted as a therapeutic management. This can greatly reduce the burden of disease in long COVID patients which is still a significant complication.[6]

Rasmussen *et al*. conducted a RCT including 28 participants, intervention (n = 14) and control (n = 14). The intervention group underwent supervised HIIT-based exercise programs for a 12-week duration. The inclusion criteria were patients confirmed COVID-19 by PCR more than 4 weeks and <6 weeks, aged ≥40, patients with atrial fibrillation and flutter, acute myocarditis, and those undergoing treatment with interleukin (IL)-6 receptor antagonists such as tocilizumab and sarilumab. The outcomes indicated that the intervention

Table 4: pVO_2 max values and the heart rate max values in each study conducted and the mean differences between the rehabilitation (intervention) group and the control group.

Authors	VO_2 peak (ml/kg/min)			Heart rate max (beats/ min)		
	Rehabilitation	Control	Mean difference	Rehabilitation	Control	Mean difference
Mcnarry *et al.*[6]	42	36.8	5.2	Not available	Not available	Not available
Rasmussen *et al.*[7]	27.8	24.7	3.1	Not available	Not available	Not available
Jimeno-Almazan *et al.*[8]	38.9	36.1	2.8	144	135	9
Longobardi *et al.*[9]	22.2	21.3	0.9	154	143	11
Palau *et al.*[10]	18.9	18.8	0.1	136	140	-4
	Total mean difference		2.42	Total mean difference		5.33

group showed a significant increase in LVM by MD of 3.1 and $P = 0.04$. The data were were not statistically significant due to high variability and insufficient statistical power despite the improvement in cardiorespiratory fitness (VO_2 peak).[7]

Increased VO_2 peak reflects the improvement in cardiorespiratory fitness.[11,12] No improvement in pulmonary function, such as diffusing capacity for carbon monoxide (DLCO) suggested that post-COVID lung changes were primarily associated with fibrosis and resistance to any modifications.[13]

Jimeno-Almazán *et al.*, performed a RCT involving concurrent training at low and moderate intensity as an intervention whereas the control group followed general rehabilitation care according to the WHO guidelines.[8] The study showed notable improvements in VO_2 max by an average of 2.1 ml/kg/min, which was clinically translating into better results in cardiopulmonary health.[14,15] In addition, 83.3% of patients reported relief in symptoms as compared to 5.4% standard care group. There was a reduction in heart rate (HR = 13.3%) and perceived exertion, indicating improved cardiovascular health. The control group has not experienced same level of improvement reflecting the superiority of the tailored exercise program over general rehabilitation in addressing cardiac and respiratory issues.[16]

A similar outcome noted in a study conducted by Palau *et al.* included home-based inspiratory muscle training (IMT) program as an intervention. The trial receded a significant enhancement in HR response suggested that IMT had positive effects on autonomic regulation and overall cardiac function. The study showed a significant increase in VO_2 peak by 0.1 ml/kg/min, ventilatory efficiency increased by 18.9%, better performance and reduced breathlessness in long COVID patients, and the increase in the percentage of DLCO 72.8% showed improvement in lung function and breathing patterns during hyperpnea.[10] These results align with both Rasmussen *et al.* and Jimeno-Almazán *et al.*[7,8]

A study by Mcnarry *et al.* showed that VO_2 peak was increased by 5.2 ml/kg/min (effect size = 0.43) in the rehabilitation group which was greater than the control group.[6] Similar results are seen in the study of Longobardi *et al.* (2023) where VO_2 peak (MD = 4.46) and HR max (MD = 11 bpm) increased. These interventions improved the cardiovascular fitness in COVID-19 patients compared to the control group as they had a positive effect on the respiratory endurance and sufficiency as well as on the heart rate.[9]

These findings aligned with the results of the study of Nantakool *et al.* which showed that the beneficial effects of exercise rehabilitation programs on the cardiopulmonary fitness in post-COVID-19 patients. These improvements could possibly be explained by the mechanism of central and peripheral adaptations, for example, the increase in endothelial functions and arterial compliance as well as an improved cardiac reserve.[13]

A study by Torres and Gradidge showed that rehabilitation programs significantly improved the cardiopulmonary functions in patients post-COVID-19 as compared to the control group. However, this systematic review did not consider the effect of the COVID vaccine on these patients, and hence, it could be a possible confounding variable.[12]

Thirupathi *et al.* showed that exercise intensity should be prescribed to COVID-19 patients according to the severity of the disease to obtain maximum benefit instead of causing adverse physiological effects. It also revealed that low-to-moderate exercise intensity showed good results in mild to moderate COVID-19 patients.[17]

An observational quasi-experimental study by Szarvas *et al.* showed that post-COVID-19 patients benefitted from the complex cardiopulmonary rehabilitation programs and improved their quality of life. These programs also improved the exercise tolerance of these patients with an adaptation of the cardiovascular system.[18] A study by Nopp *et al.* concluded that daily individualized interdisciplinary rehabilitation programs for 6 weeks could improve the quality of life, decrease dyspnea, and increase walking capacity in 58 patients suffering from severe post-COVID-19 syndrome.[3]

A narrative review by AkbariRad *et al.* recommended that cardiopulmonary rehabilitation is a necessity in the

management of COVID-19 patients, especially those who were admitted in the intensive care unit. It also revealed that these rehabilitation programs could alleviate the development of complications, reduce mechanical ventilation time, the risk of being readmitted, mortality rate, and the length of the hospital stay. This aligned with the results of this study that the purpose of cardiopulmonary rehabilitation programs is to improve physical recovery from post-COVID-19 complications.[19]

Many studies have emerged to understand the post-COVID-19 long-term impacts on the cardiovascular and respiratory systems individually but few studies have been done to study the simultaneous effect of these rehabilitation interventions on cardiac and respiratory systems. More studies are required to devise new management strategies to reduce these aftermath effects, but larger and better-defined RCTs are needed to understand the details of exercise rehabilitation programs on both cardiac and pulmonary systems.[20,21]

Aerobic exercises such as walking (e.g., a 6-min walk and brisk walking) or cycling enhance cardiovascular and respiratory functioning as it increases the stroke volume, cardiac output, and lung volume, which leads to the reduction of the heart's workload and improves the blood circulatory system, optimizing oxygen delivery and ventilation-perfusion matching. These adaptations increase the cardiac efficiency and allow a higher HR max during physical activity while reducing excessive heart rate.

Regular exercise training also strengthens respiratory muscles, attenuates dyspnea, and raises VO_2 peak, which reduce systemic inflammation and provide an anti-inflammatory effect that shows improvement in vascular health. It supports cardiac function and prevents further damage to lung tissues. For post-COVID individuals, exercise helps in balancing the autonomic and reducing inflammatory markers such as C-reactive protein and IL. Through these mechanisms, exercise rehabilitation programs benefit cardiovascular and respiratory health.[22,23]

CONCLUSION

The SARS-CoV-2 pandemic has affected a huge number of people worldwide since 2019 and its ongoing impacts are still being seen among many COVID-19 survivors. The intervention programs in this systematic review have shown considerable progress in improving cardiovascular and respiratory health conditions. The analyses validate and fill the research gap by bringing into consideration the effectiveness of comprehensive exercise rehabilitation programs, treating both the aspects of cardiac and respiratory complications andresulting in long-term recovery. Future research should prioritize the development of effective rehabilitation programs that address the cardiopulmonary complications. This review highlights exercise-based rehabilitation interventions as one of the most effective solutions to reduce the chronic symptoms and strengthen both the cardiac and respiratory health in post-COVID-19 patients.

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Declaration of patient consent: Patient's consent was not required as there are no patients in this study.

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