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Exercise modulates the immune system in cardiorespiratory disease patients: Implications for clinical practice during the COVID-19 pandemic

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ABSTRACT

Background: Patients with cardiorespiratory problems often suffer from systemic inflammation. Stress due to the disease and continuous inflammation can undermine the success of the rehabilitation program.

Objective: This review has been undertaken primarily to understand the effectiveness of exercise training on the immune system in individuals undergoing cardiorespiratory rehabilitation and its implications for further management during the COVID-19 pandemic.

Methods: Assessors analyzed related studies identified in the MEDLINE, PROQUEST, PUBMED, Cochrane Library, CINAHL, EMBASE, Google Scholar, Physiotherapy Evidence, and Science Direct databases. The studies were divided into groups focused on the effect of exercise on blood leukocytes, the anti-inflammatory effect, and the role of nutrition and exercise in resolving inflammation.

Results: Twenty-eight studies were included in this review. The number of studies included in each section was as follows: the effects of exercise training on leukocytes in cardiorespiratory conditions ($n = 8$), anti-inflammatory effect ($n = 6$), and the role of nutrition and exercise in resolving inflammation ($n = 14$). The bias risk assessment showed poor internal validity; most included studies were assigned no and unclear descriptors.

Conclusions: Substantive evidence is presented that emphasizes the role of moderate-intensity exercise in boosting the immune system in patients with cardiorespiratory diseases. Exercise has anti-inflammatory effects that are vital for overall well-being and resolving longstanding inflammation. Individuals with an active lifestyle had a better pathogen immune response than more sedentary individuals. Our findings highlight the current need to investigate the long-term effects of cardiorespiratory rehabilitation programs.

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Introduction

Cardiorespiratory diseases are often considered the primary causes of mortality and morbidity, diminishing patients' quality of life.¹ The health-related economic burden cardiovascular disease (CVD) imposes on individuals remains unknown, including the personal liabilities of their families¹ and healthcare organizations.² The burden of pulmonary diseases has also increased in recent years worldwide. Chronic obstructive pulmonary disease (COPD) and asthma contribute significantly to a population's mortality rate.³

Rehabilitation is an integral part of remediation for disabling sequelae of cardiorespiratory diseases. The rehabilitation path for

cardiorespiratory diseases involves acute care continued in outpatient and community settings based on the complexity of the patient's need. Recently, the global coronavirus disease 2019 (COVID-19) outbreak has posed unprecedented challenges in providing rehabilitation, including for cardiorespiratory diseases.⁴

Exercise management is considered an economical and lifesaving therapy for cardiorespiratory diseases with long-term impacts on patient health.^{5,6} The remote management of pulmonary diseases using home-based rehabilitation has a beneficial aerobic capacity.⁷ The type, intensity, frequency, and duration of exercise can bring about acute and chronic effects on cardiorespiratory disease sequelae.⁸ Additionally, an optimized exercise workout provides a cohesive physiological response, improving the exercise tolerance capacity of cardiorespiratory disease survivors.⁸ Moreover, decreased exercise capacity is an independent indicator and predictor of

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numerous noncommunicable diseases, such as cardiovascular and chronic respiratory diseases.⁸

Endothelial function is a vital factor in cardiorespiratory health, a major determinant of which is the immune system. A growing body of evidence shows that exercise and nutrition can influence immune system function.

The body's defenses mainly encompass the inborn (innate) and adaptive immune responses.⁹ The innate immune system remains active from birth, with physical barriers, macrophages, and natural killer (NK) cells as primary constituents. The adaptive immune system relies more on cellular and humoral responses.⁹ The immune system is sensitive to short- and long-term exercise training. It has become evident that moderate-intensity exercises enhance immunosurveillance with several health benefits.¹⁰ Therefore, current evidence support the connection between regular physical activity and increased immunosurveillance capacity, enhancing the body's defense mechanism against infection.⁹

Short- and long-term systematic exercises can considerably modulate an individual's immune protection with additional benefits such as psychological motivation and reductions in weight and any pre-morbid inflammatory status.^{11,12} Studies have previously shown the effectiveness of pulmonary rehabilitation (PR) programs on biomarkers such as fibrinogen and albumin, which have predictive ability for the postoperative outcome of lung-related problems.¹³

Exercise's anti-inflammatory and antioxidative effects on the skeletal muscles, adipose tissue, cardiovascular system, and immune system have already been shown. It has also been postulated that exercise reduces redox-sensitive transcription factors, proinflammatory cytokine profiles, and activator protein-1.¹⁴ In addition, some studies have reported that the degree of inflammation in cardiorespiratory-related problems is related to workout intensity. However, there remains uncertainty in these results.^{15–18} In contrast, other studies have found that physical activity's amelioratory effects on cardiorespiratory problems¹⁹ and interval training's positive effects are better than other types of training.

Nutritional intervention is also essential to boost immune surveillance and the success of cardiorespiratory rehabilitation.^{20,21} A systematic review reported that regular fruit and vegetable consumption over long periods positively affects lung function in COPD individuals. Some nutritional studies have also shown the effects of dietary interventions on health-related quality of life, systemic inflammation, and physical functions.²¹ While disparities in clinical trials remain, there continues to be a need to examine the long-term effects of dietary interventions.

This integrative literature review primarily focuses on understanding the effectiveness of exercise in modulating the immune responses of individuals undergoing cardiorespiratory rehabilitation and its implications for patient management during the COVID-19 pandemic.

Methods

We performed a comprehensive and thorough search of the MEDLINE, PROQUEST, Cochrane Library, PUBMED, CINAHL, EMBASE, Physiotherapy Evidence (PEDro), Google Scholar, and Science Direct electronic databases. We used search strings combining keywords and medical subject headings terms related to exercise, nutrition, impact on the immune system, blood parameters, anti-inflammatory effects, and cardiorespiratory diseases. Studies explicitly discussing the antioxidative anti-inflammatory role of exercises and the effects of exercise on blood parameters, nutrition, and acute and chronic immune responses were included in this review. Evidence was retrieved on exercise's role, which was then used to devise a plan for its management and practice with cardiorespiratory diseases during the COVID-19 pandemic. A graphical abstract for the current review is presented in Fig. 1. Bias risk was assessed using Cochrane's risk of

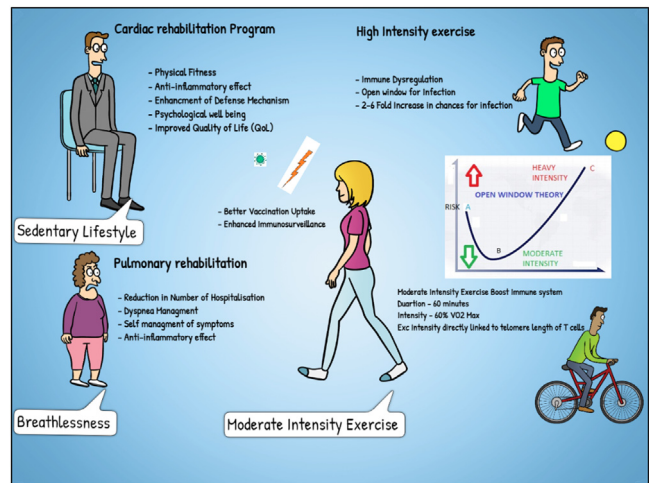


Fig. 1. Summarizing the effect of exercise in cardiorespiratory disease.

bias tool in Review Manager v.5.4.1 to rate the quality of articles included in this study (Fig. 2). The Risk of bias evaluation was divided into domain allocation concealment, random sequence generation, blinding of participants, blinding of outcome data, incomplete outcome data, selective reporting, and other biases. Yes, no, and unclear descriptors were used to report each domain.

Results

Twenty-eight studies were included in this review. This study is divided into four themes: the impact of exercise training on blood parameters, high and moderate-intensity exercise training in cardiorespiratory diseases and their immune responses (Tables 1 and 3), anti-inflammatory effects of exercise training in cardiorespiratory diseases (Table 3), and the role of nutritional interventions in cardiorespiratory rehabilitation (Table 2). The number of studies included in each section was as follows: the effects of exercise training on leukocytes in cardiorespiratory conditions ($n = 8$), anti-inflammatory effect ($n = 6$), and the role of nutrition and exercise in resolving inflammation ($n = 14$). Furthermore, facts supporting exercise's involvement in modulating the immune response were also examined.

The bias risk assessment showed poor internal validity; most included studies were assigned no and unclear descriptors in most domains. The details of the bias risk assessment are shown in Fig. 2.

Impact of exercise training on blood parameters

While moderate-intensity exercises enhance the immune system, vigorous exercises can suppress the immune system.²² Acute training leads to increased neutrophil concentration during and after exercise. Similarly, moderate exercise can increase lymphocyte counts. Intense exercise did not affect lymphocyte count.²²

Physical activity induces neutrophilia under cortisol's influence. Neutrophil chemotaxis is substantially decreased without a reduction in bactericidal activity during the post-exercise period (nearly 24 h).⁹ This decrease in neutrophil chemotaxis reverses within 48 h post-exercise. However, it should be noted that infectious microorganism activity can increase during this period.⁹

It is believed that six-week moderate-intensity exercise can also increase erythropoiesis, increasing the red blood cell and plasma volumes.²³ Finally, an eight-week structured exercise program resulted in a temporary increase in circulating plasma volume and plasma erythropoietin concentration and a gradual increase in red blood cell volume.²⁴

	Allocation concealment?	Random Sequence generation	Blinding of Participants	Blinding of Outcome data	Incomplete Outcome data	Selective reporting	Other Biases
Ahmad T 2014		+			+		
Boas SR 2000						-	
Conraads V 2002	-	-	-	-			
Darmian MA 2022	-	+	-		+		
Davidson WJ 2012							
Gielen S 2003		+					
Jenkins AR 2020							
Kitzman DW 2013	-	+	-	+	+		
Larsen AI 2001			-	-			
Larsen AI 2002	-	-	-	-			
Mercken EM 2005	-	-	-				
Nguyen T 2012							
Normandin E 2013		+			-		
Pinho RA 2007				+	-	+	-
Spruit MA 2005	-	-		-	+	-	-
SR Boas 2000							
Tirakitsoontorn P 2001			-	+	-		
Van de Weert-van 2014							
van Helvoort 2007							
van Helvoort HAC 2005							
Van Helvoort HAC 2006							
Vogiatis I 2007	-	+	-		-		

Fig. 2. Risk of bias assessment for the included studies on exercise training in cardiorespiratory conditions (Descriptors: + - yes, - No, □ - Unclear).

The innate and adaptive immune system

The body's defense is a multifaceted organization of organs, tissues, and cells.²⁵ This multidimensional system acts on unrecognized foreign bodies or molecules (e.g., parasites, bacteria, viruses, fungi, and infected cells) to eliminate them from the body.²⁵ The body's defense or immune system can be divided into innate and adaptive immunity.

Innate immunity

This immune system is typically the primary defense mechanism against foreign pathogens. It typically comprises immune cell-like monocytes, macrophages, granulocytes, and NK cells.²⁶

Acquired immunity

The primary purpose of adaptive immune responses is to recognize specific antigens by differentiating antigens.²⁷ The adaptive immune system mainly comprises T and B cells, which produce antibodies against unrecognized foreign bodies.²⁷

High and moderate-intensity exercise training in cardiorespiratory diseases and their immune responses

Effect of exercise on the innate and adaptive systems

Ample evidence suggests that regular moderate-intensity exercise enhances innate immune function.²⁸ In contrast, acute high-intensity or regular, intense exercise can disrupt the defense mechanism, increasing the risk of upper respiratory tract infection.²⁸ Evidence suggests that intense training sessions increase the likelihood of infection, relapse, and myocarditis. Macrophages, NK cells, and neutrophils are relatively responsive to acute exercise sessions. With chronic exercise training, the NK cells show increased inactivity. In contrast, opposite or suppression inactivity is observed in neutrophil functions with intense sessions. Evidence suggests that acute moderate exercise sessions with a duration <60 min and intensity <60% of VO₂ max (oxygen uptake) are associated with reduced immune system stress.²⁸

Intermittent training is an aerobic training strategy that uses either rest or low-intensity-exercise periods between high-intensity periods. The primary concept behind this strategy is to allow more rigorous exercise periods than continuous high-intensity exercise.²⁹ Acute high-intensity interval training usually destabilizes the immune system, but chronic functional bouts may lead to immune system adaptations without altering leukocyte count.²⁹

An acute exercise period may induce distinctive temporary biphasic variations in circulating lymphocyte numbers.³⁰ Classically, high lymphocyte counts are observed throughout continuous training and immediately afterward, with fewer cells post-workout during the early recovery phase. This typical cell orchestration is commonly observed for T cells and, to a lesser extent, B cells.³⁰

Studies have found that acute maximal exercise may lead to leucocytosis in younger (~22 years) and older (~65 years) adults.³¹ An increase in both CD4+ and CD8+ lymphocytes is observed post-exercise. Despite high CD3+ cell accumulation, lymphocyte production is often reduced in the aged. Therefore, exercise-induced leucocytosis is observed in younger and older individuals but less often in the aged.³² Additionally, training intensity tends to be related to the telomere length for CD4+ and CD8+ T cells.³²

Table 1 discusses the exercise training results on leukocytes in cardiorespiratory conditions.

Exercise-related immunity and its J-shaped hypothesis

Regular exercise can induce adaptations, modifying each arm of the immune system depending on exercise intensity.³³ However, factors such as sex-related differences, age, nutrition, and psychological stress might also play an influential role.

This J-shaped curve explains the association between exercise intensity and infection susceptibility.³⁴ This hypothesis advocates that medium-intensity workouts can enhance the body's defense mechanism in inactive individuals, while high-intensity workouts may weaken the body's defense mechanism.³⁴ Niemen et al. previously used this hypothesis to explain the 2–6-fold increase in the risk of developing respiratory infections among marathon runners.³⁴

Mounting research evidence advocates that athletes involved in vigorous workouts are more likely to develop upper respiratory tract

Table 1
Effects of exercise training on Leukocytes in cardiorespiratory conditions.

Authors	Design	Condition	Group		Type of training	Duration	Evaluation		Outcome measure	Reported Result	Reported Adverse Events	Number of Exacerbations	Adherence with Intervention
1. Van Helvoort HA et al ⁷⁹	Case-control	COPD	Intervention (n=) COPD=7	Control (n=) Nonsmoking healthy participants =10	Maximal intensity exercise	Total duration of 8–12 min with gradual increases in the workload till exhaustion	Pre Post	Pre Post	Total Leukocytes	Leukocytosis observed at the initial phase, especially neutrophils raise with drop in lymphocyte count at later stages	Not reported	Not reported	Unclear
2. Van Helvoort HA, et al ⁸⁰	Case-control	COPD	COPD=16	Healthy=11	Maximal intensity exercise followed by sub-maximal intensity exercise after a week	Single session bicycle ergometer With initial 3 min without loading later gradual increments in the load till exhaustion	Pre	post	Total Leukocytes	The observed leukocytosis not related to the intensity of exercise (maximal and sub-maximal exercise)	Not reported	Not reported	Unclear
3. Davidson WJ, et al ⁸¹	Pre-post	COPD	COPD=20	–	Incremental exercise	Single session bicycle ergometer With initial 2 min without loading later gradual increments in the load till exhaustion	Pre	Post Post 2 h Post 24 h	Neutrophils,% Eosinophils,% Macrophages,%	Short term session of incremental exercise, causes increased eosinophils, phlegm in patients with COPD, with no noteworthy variations in other inflammatory cells	No adverse events	Not reported	Unclear
4. Jenkins AR, et al ¹⁶	Pre-Post	COPD	COPD=40	–	Cardiorespiratory fitness and strengthening exercises	Single session consists of exercise and education for 2 h, 2 sessions per week for 8 weeks	Pre	post	Total / differential cell counts and neutrophil activation markers, maturity markers, suppressive, immature, progenitor,	Leukocytosis observed at the initial phase, especially rise in the neutrophils count	Unclear	Due to aggravations of symptoms three participants discontinued	Unclear

(continued on next page)

Table 1 (Continued)

Authors	Design	Condition	Group		Type of training	Duration	Evaluation		Outcome measure	Reported Result	Reported Adverse Events	Number of Exacerbations	Adherence with Intervention
5.Nguyen T, et al ⁸²	Case-control	Cystic fibrosis	Cystic fibrosis= 12	Healthy= 12	Moderate intensity exercises followed by high intensity exercises, providing 30 min interval between two modes of exercise	Single session of moderate-intensity exercise characterized by 2 sessions of exercises done at 50% of maximal power with 6 min of rest period between each session. Whereas high intensity exercise comprises of 6 short sessions done at 100% of maximal power with 1 min of rest between each session	Pre	post	Leukocytes Neutrophils Lymphocytes Monocytes	The prescribed exercise pattern couldn't notice any changes in leukocytes but, reported increase in growth hormones	Not reported	Not reported	Unclear
van de Weertvan, et al.(83)	Longitudinal study	Cystic fibrosis	Cystic fibrosis=13	–	Callisthenic and aerobic exercises	Patient advised to perform 11 min of five Callisthenic exercise and aerobic exercises for 12 weeks at home	Pre	post	Leukocytes	In addition to leucocytosis large amount of inflammatory cytokines production causes adverse effects on muscles	Unclear	Unclear	Unclear
6.Boas SR, et al ⁸⁴	Case-control	Cystic fibrosis	Cystic fibrosis=15	Healthy= 15	Aerobic activity	Exercise load progressed gradually considering the participant's anthropometrics	Pre	post	Total Leukocytes Granulocytes Lymphocytes Monocytes	The immediate cellular response to exercise is normal	Not reported	Not reported	Unclear
7.Boas SR, et al ⁸⁵	Case-control	Cystic fibrosis	Cystic fibrosis=12	Healthy= 12	Aerobic activity	Exercise load progressed gradually considering the participant's anthropometrics	Pre	post	Total Leukocytes Granulocytes Lymphocytes Monocytes	The observed post-exercise leukocytosis was indistinct in cystic fibrosis	Not reported	Not reported	Unclear
8.Van Helvoort HA, et al ⁸⁶	Pre-post	COPD, ex-smoking patients with muscle wasted	COPD=10	–	6-min walking test (6MWT) Maximal cardiorespiratory exercises testing (CPET)	As per ATS (American Thoracic Society) guidelines	Pre	post	Leukocytes Neutrophils Lymphocytes Monocytes	6MWT showed less initiation of circulating inflammatory cells to CPET	Not reported	Not reported	Unclear

COPD- Chronic obstructive Pulmonary disease, n-number.

Table 2
Effect of nutrition and exercise on inflammatory markers post cardiorespiratory rehabilitation.

Authors	Design	Group		Type of nutritional intervention	Type of physical activity	Evaluation		Outcome measure	Reported result	Reported Adverse Events	Number of Exacerbations	Adherence with Intervention
		Intervention (n=)	Control (n=)			Pre	Post					
1.Ford et al ⁸⁷	Cross-sectional		13,748	Vegetables and fruit intake (times per month)	Self-reported	–	–	C-reactive protein in cardiovascular disease	Positive role in subsiding inflammation	–	–	–
2.Sugawara et al ⁸⁸	RCT	17	14	Nutrition supplementation	Home-based low-intensity PR program	0 wk.	12 wk.	CRP, IL-6,8, TNF- α , MRC, PI max, 6MWD, quadriceps muscle force	Exercise combined with anti-inflammatory nutritional supplement shows an resolatory effect in elderly with stable COPD	Not reported	Unclear	Unclear
3.Roca-Rodríguez et al ⁸⁹	Prospective cohort	26		Mediterranean diet	Outpatient Cardiac rehabilitation	0	8 wk.	IPAQ, biochemical variables like IL-1, IL6, Lipid profile, Leptin and adiponectin	No changes in the inflammatory status	Not reported	Unclear	Unclear
4.Tung LF et al ⁹⁰	RCT	27	27	Nutritional education	High Flow nasal therapy + Exercise Limb strength training, and ergometer bicycle training			Pulmonary functions, Arterial blood gas analysis, WBC and CRP	Increases exercise tolerance and reduces systemic inflammation in	1 event	No change in number of Exacerbations Post Interventions	Not reported
5.Beckie et al ⁹¹	RCT	48	43	Dietary Counselling and Modifications	Combined aerobic exercise and upper body resistance training. Aerobic exercise consisted of (treadmill walking, cycling, or rowing) with intensity 60–85% of maximal heart rate	0 wk.	12 wk.	CRP, Intercellular adhesion molecule-1 (ICAM-1), (IL-6), and TNF- α	Gender based-CR and Traditional CR were effective in reducing inflammatory biomarkers		Unclear	Unclear
6. Caulin-Glaser et al ⁹²	Retrospective cohort analysis	172		Nutritional Education	Cardiac Rehabilitation	0 wk.	7–8 wk.	Fasting blood sample for lipid profile, CRP, and glucose	Decrease the level of CRP regardless of gender, age, or presence of metabolic syndrome	Unclear	Unclear	Unclear

Table 3

A qualitative view of anti-inflammatory effect of exercise training in cardiorespiratory conditions.

Authors	Study design	Condition	Outcomes related to anti-inflammatory effects	Reported results
1.Normandin et al ⁹³	Unclear (N = 20)	CHF	C-reactive proteins, Cardiac troponin T (cTnT) and brain natriuretic peptide (BNP)	Neither high intensity Interval exercise nor moderate-intensity continuous exercise caused any significant change in CRP, BNP, or cTnT levels
2.Gielen S et al ⁹⁴	RCT (Exc=10; Con=10)	CHF	Interleukin (IL)–6, and IL-1-beta levels, Serum tumor necrosis factor (TNF)-alpha, local cytokine, and iNOS expression	Exercise training significantly reduced the local expression of TNF-alpha, IL-1-beta, IL-6, and iNOS in the skeletal muscle of CHF patient
3.Conraads et al ⁹⁵	Non randomized (Exc=23; Con=18)	CAD/IDCM	Interleukin (IL)–6, tumor necrosis factor (TNF)-alpha, soluble TNF receptor 1 (sTNFR1) and 2 (sTNFR2)	Exercise training has an anti-inflammatory effect in patients with CHD and CAD
4. Darmian et al ⁹⁶	RCT (Exc+TS (n = 11), Exc+placebo (Exc; n = 10), TS (n = 11), and Con (C; n = 10)	HT2DM	hs-CRP levels, HDL, cholesterol, and TG	Exc + TS is recommended as a conclusive lifestyle approach to manage metabolic status, oxidative stress biomarkers, and CRP in middle-aged females with T2DM
5.Larsen et al ⁹⁷	Pre-Post (n = 28)	CHF	TNF-alpha, IL-6, IL-8	Present study demonstrates that aerobic exercise training reduces pathologically increased TNF- alpha levels in patients with CHF
6. Kitzman et al ⁹⁸	RCT (n = 63) Exc=32, Con=31	CHF	B-type natriuretic peptide (BNP), Carotid stiffness index, Brachial FMD	Exercise training didn't alter endothelial functions or arterial stiffness
7.Larsen et al ⁹⁹	Pre-Post (n = 15)	CHF	Muscle biopsies, TNF-alpha, IL-6, IL-8	Increase in muscle fiber area%. Moderate negative correlation between the level of interleukin 6 and fiber thickness at baseline,
8.Ahmad et al ¹⁰⁰	RCT n = 928 Exc=477, Con=451	CHF	Plasma levels of amino-terminal pro-brain natriuretic peptide (NT-proBNP), high- sensitivity C-reactive protein (hs-CRP), and cardiac troponin T (cTnT)	A 12-week exercise training program did not lead to improvements in plasma concentrations of cytokines nor NT-proBNP, when compared with usual care
9. Vogiatzis et al ¹⁰¹	Pre-post, COPD n = 15	COPD	Muscle Biopsies, TNFa, C-reactive protein (CRP), tumor necrosis factor-a (TNFa) and (C) interleukin-6 (IL-6)	Pulmonary rehabilitation induced muscle adaptations and skeletal muscle hypertrophy without decreasing the levels of systemic or local muscle inflammation
10. Rabinovich et al ¹⁰²	Case control, COPD (n)= 11, Con =6	COPD	TNF-a, soluble TNF receptors (sTNFRs: sTNFR55 and sTNFR75) and interleukin (IL)–6 and TNF-a mRNA	Moderate-intensity exercise increases plasma tumor necrosis factor-a levels in COPD without exercise-induced upregulation of the tumor necrosis factor-a gene in skeletal muscle
11.Nguyen et al ⁸²	Case control, CF(n)= 12, Con=12	Cystic fibrosis	IL-6, TNF- α , GH, and IGF-1	High Intensity, Intermittent exercise of adequate intensity can increase GH in children with CF, without affecting systemic inflammation, whereas Continuous mode of moderate-intensity exercise is associated with significant increase in IL-6 levels
12.Spruit et al ⁷⁷	Open prospective intervention study, Exc (n)=78	Advanced COPD	CRP, TNF- α , sTNFR-p55, sTNFR-p75, and IL-8	No change in CRP post-training, but other factors had a significant change post-training
13. Pinho et al ¹⁰³	Unclear, n = 15. Exc =8 and Con = 7	COPD	Index of lipid peroxidation, thiobarbituric acid reactive species (TBARS), total radical-trapping antioxidant parameter (TRAP) and xanthine oxidase (XO) activity	PR program is associated with decreased systemic exercise-induced oxidative damage
14. Mercken et al ¹⁰⁴	Case-control (n)=22, Exc =11, Con=11	COPD	Urinary MDA, H ₂ O ₂ in breath condensate	8 week PR program is related to increased exercise capacity and reduced exercise-induced oxidative stress

CHF- Cardiac Heart failure, cTnT – cardiac troponin, Coronary artery disease (CAD) or idiopathic dilated cardiomyopathy (IDCM), TS-turmeric, Hyperlipidemic Type 2 Diabetes Mellitus (HT2DM), C-reactive protein (CRP), hs-CRP- high- sensitivity CRP, TG- Triglycerides, HDL-High- Density Lipoprotein, FMD = flow-mediated arterial dilation, IL- Interleukin, TNF- α - Tumour Necrosis factor-alpha, Soluble tumor necrosis factor receptor (TNF), Placebo- no treatment, PR- Pulmonary rehabilitation, Exc= exercise training, Con= Controls, MDA- malondialdehyde, H₂O₂- Hydrogen peroxide in breath condensate, GH- growth hormone, COPD- Chronic obstructive pulmonary disease, idiopathic dilated cardiomyopathy-IDCM, CAD- coronary artery disease, CHF- chronic heart failure, HT2DM- Hyperlipidemic Type 2 Diabetes Mellitus, MDA- malondialdehyde.

infections.³⁵ After long periods of intensive exercise, the immune system may experience physiological stress and suppression. This period is called an “open window” and usually lasts 3 to 72 h. Therefore, the host remains vulnerable to microbes and pathogens such as bacteria and viruses, with a greater likelihood of contracting infections.²⁵

Therefore, advocating exercise training in cardiorespiratory disease, especially high-intensity exercises, may require caution and knowledge about the J curve theory since patients with cardiorespiratory diseases are already susceptible to infections. However, if the exercise training program does not attain the desired intensity, it may fail to produce the required effects on the body's inflammatory state.³⁶

Role of nitric oxide (NO) in inflammation and exercise

NO plays a key role in defense systems protecting against infections by various organisms. It differentiates the growth and death of immune and inflammatory cells, which include mast cells, macrophages, neutrophils, NK cells, and T lymphocytes.³⁷ One study found that four weeks of home-based exercise training enhanced the release of endothelium-derived NO in hypercholesterolemic patients without altering risks for other comorbidities. Therefore, current evidence indicates that exercise training has both cardioprotective and blood pressure normalizing effects.³⁸

The anti-inflammatory effects of exercise training in cardiorespiratory diseases

It is well-known that chronic build-up of inflammatory biomarkers, such as fibrinogen, C-reactive protein (CRP) and cytokines, may develop and progress toward cardiorespiratory disease.³⁹ Skeletal muscles generally interconnect with other tissues through peptides called myokines which are secreted by the myocytes during muscle contractions.³⁹ The exercising muscle usually produces and discharges several peptides, including leukemia inhibitory factor and interleukins (IL)-4, IL-6, IL-7, and IL-15.

Studies exploring exercise's role also specifically reported that exercise induces the release of myostatin inhibitors usually released from wasted or disuse muscles, which act on myostatin and negatively affect muscle mass and hypertrophy.³⁹ Exercises stimulate the release of follistatin and myostatin inhibitors from the liver.³⁹

The first cytokine released from active skeletal muscle cells into the blood during exercise is IL-6. Exercise increases the amount of muscle-derived IL-6 in the blood.³⁹ The training period is usually the primary factor regulating the extent of systemic IL-6 release.³⁹ Therefore, longer workout periods lead to a more distinctive total IL-6 release. This release of IL-6 is primarily related to workout intensity, approximately around 70%–85% of VO₂ max.³⁹

A direct relationship exists between IL-6 levels and several dependent factors such as exercise capacity, duration, and intensity.⁴⁰ Evidence from in vivo studies indicates IL-6 has beneficial effects since its deficiency can accelerate the atherosclerotic process.³⁹ In contrast, tumor necrosis factor-alpha (TNF- α) in the arteries may promote the atherosclerosis process via specific adhesion factors. Additionally, inflammatory cytokines modify skeletal muscle histology and deleteriously affect cardiac contractility and left ventricular remodeling.⁴¹

Notably, while a structured exercise training regime can adversely affect plasma IL-6 levels, muscular IL-6 receptor levels are increased, indicating improved IL-6 signaling in expert compared to amateur individuals.³⁹ Some studies discussing the resolutive effects of exercise training in cardiac and pulmonary conditions are discussed in Table 3. It should be noted that most studies listed in Table 3 report the beneficial effects of exercise.

The elevated levels of inflammation in disorders such as COPD can be resolved with exercise training regimes.³⁹ Unfortunately, abdominal adiposity and physical inactivity^{42,43} combine to create a persistent secondary exacerbated condition in the whole body. Ancillary studies support the direct association between sedentariness and visceral fat deposition.⁴⁴ Studies have identified important factors concerning the harmful outcomes of visceral fat deposition in the liver and skeletal muscles that may further accelerate systemic inflammation.³⁹

Exercise training improves cardiorespiratory fitness and anti-inflammatory effect in patients with chronic heart failure.⁷³ This anti-inflammatory effect further attenuates chronic heart failure progression. However, there remains a dearth of studies on the anti-inflammatory potential of exercise training in PR in COPD cases.⁷⁴ A prominent reason for this could be the failure to reach the optimum intensity to produce the desired blood parameter effects. In addition,

most studies failed to calculate exercise adherence for participants (Tables 1 and 2).

Role of nutritional interventions in cardiorespiratory rehabilitation

The surveillance ability of the immune system can be increased through a mild to moderate intensity exercise training regime.²⁵ In contrast, the lower immune response in the upper airway after high-intensity exercises may be due to decreased salivary and nasal release and a reduction in nasal neutrophil numbers.^{25,45} The results of nutrition and exercise interventions for cardiorespiratory problems in decreasing inflammation are discussed in Table 2. It is perhaps already known that exercise capacity is inversely associated with the body's inflammatory status.⁴⁶

Individuals following a diet combining numerous nutrients and food items experience additional cardioprotective and anti-inflammatory effects.⁴⁷ Diets rich in vegetable seeds, legumes, fruits, nuts, and whole grains, have been associated with lower inflammation.^{48–50} In contrast, diets high in meat have been associated with greater inflammation.^{51–53} The American Heart Association Nutrition Committee and the European Society of Cardiology have reported that the daily consumption of vegetables and fruits can decrease CVD risk.^{54,55}

An analysis of 83 studies (two cohort studies and 12 observational, 10 cross-sectional, and 71 clinical trials) showed that greater vegetable and fruit consumption was inversely associated with decreases in TNF- α and CRP levels and total airway inflammation.⁵⁶ Another study comprising 792 participants with a mean age of 70 years found that plant-based diets appeared superior and were associated with lower plasma fibrinogen and CRP levels.⁵⁷ A diet rich in nuts, especially walnuts and peanuts, has been shown to lower CVD morbidity and mortality.⁵⁸ Moreover, a recent meta-analysis of 23 randomized control trials assessing the effectiveness of nuts in reducing inflammation markers found that dietary management with nuts could meaningfully decrease intercellular adhesion molecule-1 and inflammatory biomarker levels.

Nevertheless, research has shown the various benefits of a vegetable-based diet. However, there remains a dearth of studies evaluating the long-term effects of dietary management programs.⁵⁹ Consequently, the long-term effects of exercise and nutrition on inflammatory and immune biomarkers must be assessed as an indicator of its long-term efficacy, simultaneously evaluating the effects on several adverse events, hospitalizations, and adherence to exercise programs (Table 2).

A conceptual basis for rehabilitation programs: their theoretical foundation in practice

Cardiac rehabilitation and PR programs are essential for people recovering from cardiac surgery, myocardial infarction, heart failure, or transplants.⁶⁰ There is increasing evidence that cardiac rehabilitation (CR) effectively decreases morbidity and mortality, increasing mental well-being, quality of life, and exercise capacity.⁶⁰

The American Association of Cardiovascular and Pulmonary Rehabilitation and the American Heart Association have reported that the essential core rehabilitation program components help reduce cardiovascular risk, augment healthy behaviors, and decrease cardiovascular-related morbidity and mortality.⁶¹ The fundamental components are exercise training, dietary counseling, assessment, psychosocial mediation, and controlling risk factors.⁶¹ Therefore, it is essential to design programs that effectively modify risky health behaviors and immunomodulation.

Similarly, PR has proven beneficial in patients with lung diseases, breathlessness, reduced functional capacity, decreased quality of life, and frequent hospital admissions.⁶² There is a current consensus that

greater physical activity intensity is associated with lower mortality from noncommunicable diseases.⁶³

However, the exact dose-response providing anti-inflammatory effects in cardiorespiratory disease remains unknown. Moreover, some animal studies have reported enhanced acute immunosurveillance, the effect of which remains unknown in healthy and diseased populations.^{64,65} The specific concepts discussed in the current review will enhance the decision-making process when designing CR or PR programs. It is believed that exercise causes an acute increase in IL-6, which is known for its anti-inflammatory effects.¹¹ Over time, this effect can be vital for interventions focusing on patients suffering from cardiac or pulmonary diseases.

The cytokine storm in COVID-19

In moderate to severe COVID-19 infection, a destructive inflammatory reaction is often observed in which enormous quantities of proinflammatory cytokines are discharged, called a cytokine storm.⁶⁶

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; also known as 2019-nCoV) infected individuals show an enhanced response leading to an unwarranted adverse reaction in the body. Greater cytokine quantities are released in severe COVID-19 cases, including interferon-gamma IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-17, TNF- α , gamma-induced protein 10, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha, and granulocyte-colony stimulating factor. This enhanced response can cause an auto-immunological attack, causing extensive damage to the primary organs such as the heart, lung, brain, and kidneys, eventually leading to multiple organ failures.⁹

COVID-19 and its ongoing impacts on cardiorespiratory rehabilitation

Wuhan became the epicenter of the COVID-19 pandemic in 2019. Scientists rapidly discovered a new coronavirus named SARS-CoV-2.²⁵ As the pandemic evolved, COVID-19 survivors began experiencing disorders or residual impairments called post-COVID-19 syndrome.²⁵ Recent data suggests that around 20% of individuals infected with SARS-CoV-2 may suffer from serious symptoms for over 12 weeks postdiagnosis. While studies have begun exploring this novel condition, the best practice for management in this field remains to be determined.²⁵

It has been reported that COVID-19 has severely obstructed CR care worldwide. A survey evaluating the impact of the COVID-19 pandemic on healthcare in 70 countries reported that it caused a temporary interruption in approximately 75% of CR programs.⁶⁷ Additionally, it should be noted that substantial psychosocial and economic impacts have affected cardiorespiratory providers.^{67,68} Therefore, CR models should promote a healthy lifestyle through home-based, virtual programs to ensure a safe, accessible healthcare system.^{67,69}

It remains advisable to evaluate exercise capacity virtually.⁶⁸ Specific tests such as the one-minute sit-to-stand test can be used to remotely assess aerobic capacity and leg strength since they are quite sensitive to changes, particularly pulmonary problems in COPD patients.⁶⁸

Evaluation of exercise responses can be made using a pulse oximeter to measure oxygen desaturation, a common finding that may become complex with COVID-19. Electronic blood pressure monitors can similarly be used. Exercise intensity can be self-evaluated using a rating of perceived exertion scale and a modified Borg dyspnea scale.⁶⁸ A walking test can also be used to evaluate cardiorespiratory fitness in patients with CVD by remotely monitoring them after administering a structured exercise program.⁷⁰ Evidence suggests that CR using a walking test and telemonitoring using a heart rate monitor can efficiently administer and increase cardiorespiratory fitness in cardiac patients with mild-to-moderate risk factors.⁷⁰ Self-

management approaches are another core aspect in the remote management of COPD and asthma, which requires the patient to have sufficient knowledge and self-care skills.⁷¹ An organized self-management strategy can decrease the number of episodes of exacerbations requiring hospitalization, improving the patient's mental, social and physical health^{71,72} during the COVID-19 pandemic.

Integrating current evidence into best practices

High-quality studies have clearly shown the beneficial effect of rehabilitation on exercise capacity, dyspnea, and physical activity post-enrolment.⁷³ Anxiety and depression could reflect different aspects of the same situation. After an appropriate referral process, the rehabilitation process should consider an appropriate support system to manage them.⁷³ Goal setting in the rehabilitation program should be patient-centered and individually tailored rather than generally applied for a specific intensity to provide beneficial results. Structured home-based PR also has beneficial effects that will be vital for remotely managing complex clinical scenarios, such as individuals with pre-existing pulmonary or cardiac problems isolating due to COVID-19.

While clinically assessing affected patients, comorbidities should be assessed as part of good practice to rule out absolute contraindications to the treatment sessions. Moreover, the exercise sessions should be modified per the assessment status in relative contraindication cases. In addition to good practices, it is essential to acquire patient suggestions and feedback to further develop the program.⁷³

Guidelines for minimizing the risk of COVID-19 infection and transmission and optimizing rehabilitation sessions

Patients with pre-existing cardiorespiratory disease exposed to COVID-19 may have a combination of complex sequelae with signs of myocardial injury, arrhythmias, and heart failure. Such patients often remain at a higher risk of mortality and morbidity.^{25,68} Patients with heart failure have reported low immune status, especially heart transplant recipients. Therefore, vaccination is a must in these patients⁷⁴ to significantly reduce their chances of exposure. However, no vaccine provides 100% protection against COVID-19.⁷⁴ Noncommunicable diseases such as diabetes and hypertension may further exacerbate the situation. Nevertheless, heart failure in recovering patients might be a potent indicator of the impending danger of death.⁷⁴

Therefore, minimizing infection or reinfection in existing patients with comorbidities is vital. It will be essential to prevent disease transmission by using a well-ventilated room, personal protective equipment (PPE), and frequently checking for temperature and symptoms. A separate room with outpatient facilities for patients already infected with COVID-19 requiring rehabilitation⁷⁵ will be of paramount importance. A high-efficiency particulate air filtration system should be used for COVID-19-infected patients, particularly during transportation. However, wearing PPE is recommended in all circumstances as the second line of control in system failure.⁷⁶ Patients hospitalized with COVID-19 symptoms should receive therapy at their bedside⁷⁷ until their situation enables discharge.

When preparing the patient for discharge, oxygen saturation, need for oxygen therapy, baseline respiratory function, and exercise capacity should be determined both at rest and during activity. A structured exercise program should always be pursued post-discharge for at least 6–8 weeks.⁷⁸ Additionally, mild-to-moderate exercises should be pursued at home with patient education, self-evaluation, and management skills with access to remote monitoring of vitals for immediate assistance, if required.^{69,78}

Once the impairments in the cardiorespiratory system are identified among the COVID-19 survivors, they should receive a complete rehabilitation program per the standards.⁷⁸ Baseline evaluation of mental and

physical health will also be essential since they may also hinder the rehabilitation program. In addition, COVID-19 survivors with disuse atrophy post-discharge should receive nutritional support.⁷⁸

Future directions

This review clearly outlines the anti-inflammatory effects of exercise-based interventions. Therefore, future trials should focus on both the short- and long-term implications of interventions in patients with cardiorespiratory diseases. Well-controlled trials are needed to understand the optimal regimen required to produce immune system effects.

Conclusions

A structured exercise program appears a prudent approach for elevating the immune status among patients with cardiorespiratory diseases. The use of exercise in these patients for its anti-inflammatory and immune-protective effects is recommended. However, high-intensity exercises should be used with caution as they can temporarily increase susceptibility to infection post-exercise. It should be noted that moderate-intensity exercises should be performed for <60 min with <60% oxygen consumption to attain maximum benefits from the rehabilitation program. While sufficient trials highlight exercise's positive effects, there remains a need to investigate the long-term effects of cardiorespiratory rehabilitation programs in pandemic situations with a better methodological design.

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Authors' contributions

The authors confirm their contributions to the paper as follows: Study conception and design: SD. Conceptualization: SD; Data curation: SD and KG; Formal analysis: SD, RR, and VN; Investigation: SD, KG, and RR; Methodology: SD, VN, and SL; Project administration: SD; Resources: SD; Supervision: SD; Writing-original draft: SD, VN, and RR.; Writing-review and editing: SD, KG, and SL. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Competing Interest

None

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Supplementary materials

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