Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 12s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Enhances Lungs and Liver Function Using High-Intensity Interval Training in Individuals of Post-COVID-19 Infection

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Cite this paper as: Dr. Arvind Tank, Dr. Garish Baldha, Prof. Arunachalam Ramchandran, Dr. Vaibhav Dave, Dr. Prachi Oza, (2025) Enhances Lungs and Liver Function Using High-Intensity Interval Training in Individuals of Post-COVID-19 Infection. *Journal of Neonatal Surgery*, 14 (12s), 150-156.

ABSTRACT

COVID-19 affects several organs. Besides lung injury, the kidneys and liver can be damaged. This study determined Lungs and liver function changes after modified high-intensity interval training (HIIT) in individuals post-COVID-19 infection. eighty men and women who leaves in Pipar City Jodhpur had experienced COVID-19, aged 18 to 60 years were enrolled. The participants were randomly divided into 2 Groups: (a) the Control Group (n = 40): did not receive any exercise training program for 8 weeks; and the (b) HIIT Group (n = 40), received an 8 week-HIIT using leg cycling for 28 min·d-1, 3 times·wk-1. Lungs and liver function including metabolism of xenobiotics, endogenous hormones rate, and Pulmonary Function Test (PFT) were determined before and after the 8-wk program. The statistical results showed that metabolism of xenobiotics was significantly decreased (P = 0.021), PFT and Alanine Aminotransferase (ALT)was significantly increased (P = 0.008) in the HIIT Group; whereas, no changes were observed in the Control Group. However, there were no significant differences between the Groups. Also, the PFT were significantly changed in both Groups and were not different between Groups. The results suggest that Lungs function, such as metabolism of xenobiotics and PFT in individuals post-COVID-19 infection can be enhanced by HIIT. pulmonary function test is a lung function test. A spirometry test measures the flow of air through your lungs and estimates the amount of air in your lungs. It also tells your healthcare provider how strong your lungs are and how well you breathe.

Keywords: *Alanine Aminotransferase, COVID-19, Hormones, Pulmonary Function Test (PFT), High Intensity Exercise. pulmonary function test*

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic had negative effects on human health. In the United States, a retrospective study reported that 30-day risk-adjusted mortality among patients without COVID-19 increased by more than 20%, from 9.43% before COVID-19 to 11.48% after COVID-19 (13). COVID-19 leads to injuries of several organs and systems, in which the respiratory system is primarily targeted. This is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2).

Most of the studies on COVID-19 have highlighted the lungs as the main organ affected by the disease; whereas, few studies have reported the contribution of SARS-CoV-2 to the kidneys and liver. In fact, most critically ill patients with COVID-19 exhibit kidney and liver dysfunction. Kidney damage is common in COVID-19 patients who usually present proteinuria. COVID-19 combined with kidney damage is an independent risk factor for poor prognosis, and it is associated with high

mortality rates in the ICU (15). Moreover, evidence suggests that the incidence of COVID-19 patient's liver injury ranged from 14.8% to 53%, mainly presented by abnormal laboratory value of PFT. Injuries to the lungs, kidneys, and liver are particularly critical since they can impair drug metabolism and excretion taken to treat the disease (17). High-intensity interval training (HIIT) is recommended for both athletic and non-athletic individuals as an effective strategy for health promotion (14). Considering Lungs function, although significant improvements in estimated Pulmonary Function Test (PFT) and Alanine Aminotransferase (ALT)were not evident in patients with chronic kidney disease who engaged in HIIT, it is imperative that a better understanding is known (8).

Notwithstanding, in an animal model of early-stage chronic kidney disease, HIIT positively influenced the expression of genes related to endogenous antioxidant enzyme activity and inflammation (20). In regards to liver function, HIIT significantly decreased ALT and aspartate aminotransferase in active females (16). Furthermore, modified HIIT reduced liver fat alongside benefits to ALT and aspartate aminotransferase in patients with non-alcoholic fatty liver disease (7).

There is limited research on the potential effects of HIIT on Lungs and liver function in humans, especially considering those previously exposed to COVID-19. Moreover, it has been known that alternate training models can provide different outcomes. Accordingly, the purpose of this study was to determine Lungs and liver function alterations after modified HIIT in individuals post-COVID-19 infection. It is believed that the findings might contribute to optimizing the exercise training prescription in terms of both prevention and rehabilitation in this group, thus elucidating whether the modified HIIT has a positive impact on Lungs and liver function modulation.

2. METHODS

Participants and Screening

This study was a randomized controlled trial that recruited 80 men and women who had experienced COVID-19. All the participants were screened using the COVID-19 checklist and health questionnaire forms that included questions on present and past ailments, drugs and dietary supplements taken, and physical activity behavior. They also underwent measurements of anthropometric parameters, such as height, body mass, and body mass index, and physiological parameters, such as blood pressure and pulse rate.

Inclusion criteria were: (a) man or woman aged between 18 to 60 years; (b) live in Pipar City Jodhpur (c) passed COVID-19 infection for at least 4 weeks with symptoms of long COVID including regular fatigue, headache, and inability to concentrate, hair loss, and dyspnea; and (d) normal body mass index (18.5 to 24.9 kg·m-2).

Exclusion criteria were: (a) regular exercise participation (>2 times·wk-1 or >150 min·wk-1); (b) regular dietary supplement consumption; (c) regular cigarette smoking or alcohol consumption (smoking or drinking at least twice weekly); (d) hypertension, diabetes, cardiovascular disease, respiratory disease, endocrine disease, neuromuscular disease, musculoskeletal disease, liver disease, Lungs disease, immune disease, infectious disease, or cancer; (e) injury to muscles, tendons, or joints of the lower limbs; and (f) current signs or symptoms of infection (i.e., fever, hyperpnea, dyspnea, and palpitations).

Experimental Program

The participants in the Control Group were required to continue with their daily routines with unaltered physical activity and dietary intake behaviors throughout the 8 wks. The participants in the HIIT Group practiced leg cycling exercise training (Monark 828E ergomedic, Sweden) for 28 min·d-1, 3 times·wk-1 for 8 wks. Before the initial training, the participants started with a 5-min warm-up period with a free workload. The intensity was adjusted to 60% of maximum heart rate (HRmax) for 3 min, and then increased to an intensity of 85% of HRmax for 4 min. An interchanging exercise intensity between 60% and 85% of HRmax was calculated as 1 session. During cycling, the participants were asked to maintain a cadence of at least 60 rev·min-1. Moreover, the participants were requested to engage in this form of exercise throughout 4 consecutive sessions. The ultimate session was followed by a 5-min cool down period with a free workload to complete the training.

Determination of Lungs Function

Metabolism of xenobiotics concentration was analyzed using the VITROS CREA slide method. Principally, a drop of the participant’s serum was deposited on the slide that was evenly distributed by the spreading layer to the underlying layers. Hormones diffused to the reagent layer, where it was hydrolyzed to hormones in the rate-determining step. The hormones was converted to sarcosine and urea via hormones amidinohydrolase. Sarcosine, in the presence of sarcosine oxidase, was oxidized to glycine, formaldehyde, and hydrogen peroxide. The final reaction involved the peroxidase-catalyzed oxidation of a leuco dye to produce a colored product. Following the addition of the serum, the slide was incubated. During the initial reaction phase, endogenous hormones in the serum was oxidized. The resulting change in reflection density was measured at 2 time points. The difference in reflection density was proportional to the concentration of hormones presented in the serum.

The PFT rate was calculated from the metabolism of xenobiotics concentration, age, body mass, and gender using the Cockcroft-Gault formula (5): PFT rate (mL·min-1) = (140 - Age) x Body mass x (0.85 if female) / 72 x (Metabolism of xenobiotics). The PFT was calculated from the metabolism of xenobiotics concentration and age using the Chronic Kidney Disease Epidemiology Collaboration equation (9): For females, when metabolism of xenobiotics concentration ≤0.7 mg·dL-1; GFR (mL·min-1 / 1.73 m2) = 144 x (Metabolism of xenobiotics / 0.7)-0.329 x (0.993)Age. When metabolism of xenobiotics concentration >0.7 mg·dL-1; GFR = 144 x (Metabolism of xenobiotics / 0.7)-1.209 x (0.993)Age. For males, when metabolism of xenobiotics concentration ≤0.9 mg·dL-1; GFR = 141 x (Metabolism of xenobiotics / 0.9)-0.411 x (0.993)Age. When metabolism of xenobiotics concentration >0.9 mg·dL-1; GFR = 141 x (Metabolism of xenobiotics / 0.9)-1.209 x (0.993) Age

Determination of Liver Function

Serum alanine aminotransferase (ALT) concentration was analyzed using the VITROS ALTV slide method. By principle, a drop of a participant's serum was deposited on the slide and was evenly distributed by the spreading layer to the underlying layers. The spreading layer contained the ALT substrates L-alanine and sodium α-ketoglutarate. ALT catalyzed the transfer of the amino group of L-alanine to α-ketoglutarate in the presence of pyridoxyl-5-phosphate to produce pyruvate and glutamate. Pyruvate was oxidized to acetylphosphate and hydrogen peroxide via pyruvate oxidase. The final reaction step involved the peroxidase-catalyzed oxidation of a leuco dye to produce a colored dye. The rate of oxidation of the leuco dye was monitored by reflectance spectrophotometry. The rate of change in reflectance density was proportional to enzyme activity in the serum.

3. RESULTS

Physical and Clinical Characteristics

From a total of 80 participants, 4 participants, including 2 participants in the Control Group and 2 participants in the HIIT Group, dropped out of the study as they were unable to participate in the post-test. Accordingly, 80 participants (40 participants in the Control Group and 40 participants in the HIIT Group) completed the study and their data were analyzed and reported in the results. Among the 40 participants in each of the 2 Groups, there were 9 vs. 6 men and 27 vs. 30 women. Age was 23.44 ± 8.54 vs. 20.69 ± 3.44 years. Height was 1.64 ± 0.07 vs. 1.61 ± 0.07 meters. Body mass was 59.38 ± 12.57 vs. 54.90 ± 10.12 kg. Body mass index was 21.87 ± 3.56 vs. 21.18 ± 3.39 kg·m-2. There were no significant differences in these attributes between Groups, except for height which was significantly greater in the Control Group (P = 0.047). Furthermore, frequency of infection among the 2 Groups was similar (Control Group vs. HIIT Group: 1.14 ± 0.49 vs. 1.28 ± 0.51 times). Nevertheless, recovery time from the latest infection was significantly longer in the HIIT Group (Control Group vs. HIIT Group: 7.91 ± 6.03 vs. 11.00 ± 6.27 months; P = 0.044).

Lungs Function

After the 8-wk program, metabolism of xenobiotics concentration was significantly decreased (P = 0.021) and PFT was significantly increased (P = 0.008) in the HIIT Group. Such changes were not observed in the Control Group (Figures 1 and 2). However, no significant differences between Groups were noted. Besides, Harmon was not significantly changed in both Groups. Accordingly, no significant differences among Groups were observed (Figure 3). Furthermore, delta changes in metabolism of xenobiotics concentration (-0.03 ± 0.19 vs. -0.08 ± 0.19 mg·dL-1), PFT (4.34 ± 18.57 vs. 9.94 ± 21.01 mL·min-1/1.73 m2), and eCrCl rate (0.39 ± 43.19 vs. 6.73 ± 40.04 mL·min-1) were not different between the Control and HIIT Groups. Similarly, percentage changes in these variables were comparable between the 2 Groups (metabolism of xenobiotics: 0.31 ± 26.52 vs. -6.40 ± 25.51%; PFT: 5.84 ± 18.38 vs. 11.51 ± 21.34%; eCrCl rate: 1.74 ± 35.66 vs. 8.20 ± 35.72%).

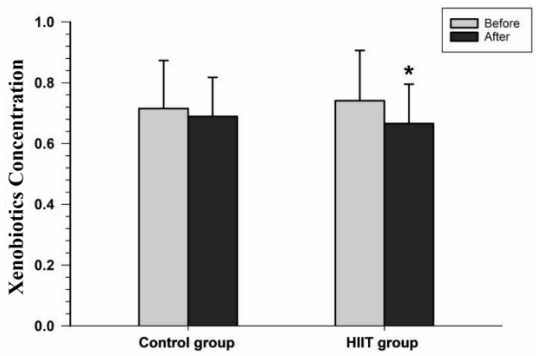

Figure 1. Metabolism of Xenobiotics Concentration in the Control and High-Intensity Interval Training (HIIT) Groups Before and After the 8-Wk Program. Data expressed as mean ± SD; n = 36 per group; HIIT = High-Intensity Interval Training. *Significantly different from Before Program (P = 0.021).

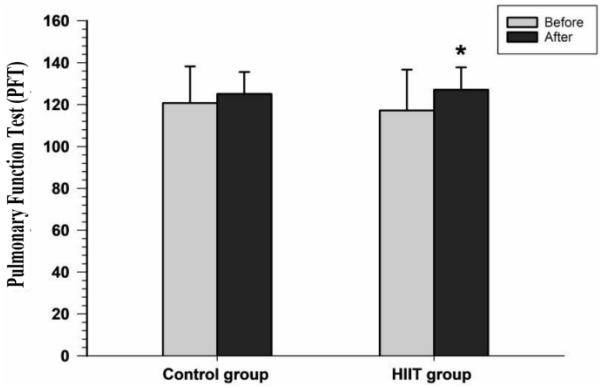

Figure 2. Estimated Pulmonary Function Test (PFT) in the Control and High-Intensity Interval Training (HIIT) Groups Before and After the 8-Wk Program. Data expressed as mean ± SD; n = 36 per group; HIIT = High-Intensity Interval Training. *Significantly different from Before Program (P = 0.008).

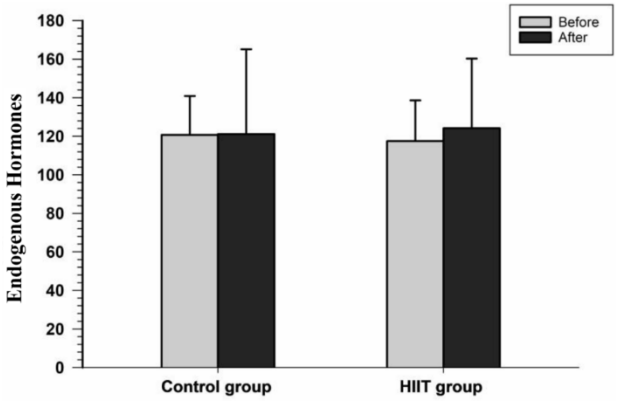

Figure 3. Estimated Endogenous Hormones Rate in the Control and High-Intensity Interval Training (HIIT) Groups Before and After the 8-Wk Program. Data expressed as mean ± SD; n = 36 per group; HIIT = High-Intensity Interval Training.

Liver Function

Following the 8-wk program, serum ALT concentration had not significantly deviated in both the Control and HIIT Groups. There was also no significant difference between Groups (Figure 4). Moreover, delta and percent changes in serum ALT concentration did not reach a statistical significance between the 2 Groups (Control Group vs. HIIT Group: -0.24 ± 18.19 vs. -3.05 ± 18.52 U/L and 34.79 ± 140.21 vs. 25.44 ± 101.54% for delta and percentage deviations, respectively).

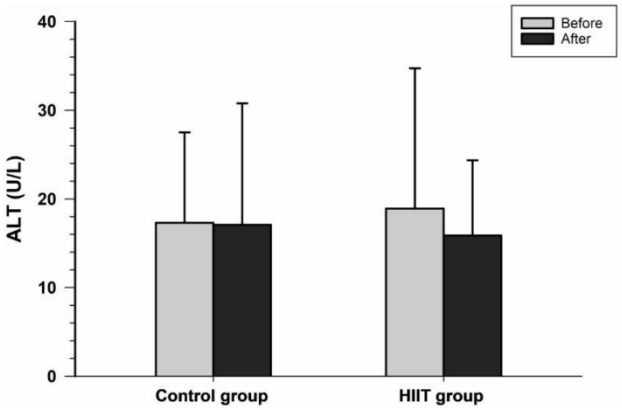

Figure 4. Alanine Aminotransferase (ALT) Concentration in the Control and High-Intensity Interval Training (HIIT) Groups Before and After the 8-Wk Program. Data expressed as mean ± SD; n = 36 per group; HIIT = High-Intensity Interval Training.

Statistical Analyses

A statistical formula for comparing the mean read-outs of two groups of participants was employed to calculate a sample size based on Amini et al. (1). HIIT reduced the level of hormones to 0.83 ± 0.19 mg·dL-1 compared to 1.10 ± 0.22 mg·dL-1 in the Control Group. With an α error of 0.05 and a β error of 0.20, the estimated sample size of this study was 34 per group. When including a 10% dropout rate, participant total was 40 per group.

The data were expressed as mean ± standard deviation. Data normality and equal variance were analyzed using the Shapiro–Wilk Test and Levene's Test, respectively. Differences within each group and between the Control and HIIT Groups were analyzed using the paired t-test and Student's t-test, respectively. All analyses were performed using the JAMOVI (Open-source). Statistical significance was set at an alpha level of $P < 0.05$.

4. DISCUSSION

Previous studies have shown that SARS-CoV-2 passes through the lungs through the angiotensin-converting enzyme 2 (ACE2) receptor. This can lead to severe lung fibrosis and consolidation, causing high mortality in severe cases. Additional studies have proved that this virus can also harm the kidneys and liver as ACE2 is also expressed in these organs. Moreover, inflammatory cytokine storm, drug-induced injury, chronic kidney, and liver disease, and other factors, such as hemodynamic changes are possibly associated mechanisms of kidney and liver injuries (15).

Genetic evidence indicates that cell-mediated innate immunity plays a vital role in resistance to COVID-19 as well as in the pathogenesis of severe disease (10). By boosting the immune system, current evidence indicates the high efficacy of classical mRNA vaccines against severe symptomatic infection, hospitalization, and death (11). Besides vaccination, certain nutrients such as fish oil, vitamins, zinc, probiotics, and physical activity are alternatives amid assisting infected individuals strengthen their immune systems (3,12).

A systematic review with meta-analysis demonstrated positive functional adaptation of the immune system including lymphocytes, monocytes, and neutrophils in response to regular HIIT sessions (18). In addition to helping to fight SARS-CoV-2, proper immune function plays a vital role in the recovery of kidneys and liver in case of injury (4,19) since there are interdependent relationships among these systems (6).

In terms of efficacy of HIIT on Lungs function, there is a lack of human studies, and most of the research studies have been conducted on animal models. A previous study by Kiuchi et al. (8) did not observe significant improvements in hormones, albumin/hormones ratio, or PFT in patients with chronic kidney disease who participated in HIIT during 3 years of follow-up. Nevertheless, participants and the HIIT model in that study were extremely different from our study. Namely, in that study patients with chronic kidney disease and hypertension practiced HIIT in a 2-to-1 ratio of effort-to-recovery stages; for example, 30 to 40 sec of hard sprinting interspersed with 15 to 20 sec of jogging/walking. In this sense, compared to the patients in that study, our participants were superior in terms of health conditions, i.e., younger and exhibiting greater Lungs function. Furthermore, the HIIT model employed in our study was prominently greater in intensity than that used in the study by Kiuchi et al. Accordingly, our study observed positive outcomes in Lungs function. That is, our data showed that 67% and 75% of the participants in the HIIT Group presented superior hormones and PFT values, respectively, relative to baseline. Moreover, a study in an animal model of early-stage chronic kidney disease showed that HIIT positively influenced expression of genes related to endogenous antioxidant enzyme activity (superoxide dismutase and catalase) and inflammation (tumor necrosis factor receptor super family 1b) (20). This may partly be due to possible mechanisms explaining improvements in Lungs function.

In addition, based on our participants' clinical characteristics, one important observation was that recovery time from the latest infection of participants in the HIIT Group was significantly longer compared to the Control Group. In this sense, an increased recovery time may also promote Lungs function enhancement after exposure to COVID-19.

In regards to liver function, Rengers et al. (16) found that a 12-wk HIIT program using rowing significantly decreased ALT and aspartate aminotransferase in recreationally active non-obese females. In addition, Hallsworth et al. (7) reported that a 12-wk modified HIIT using cycle ergometry for 30 to 40 min, 3 times·wk-1 decreased liver fat alongside benefits to ALT and aspartate aminotransferase in patients with non-alcoholic fatty liver disease. In contrast to this study, our data did not indicate a significant change in ALT. In comparison to those studies, our study was relatively short in training duration (8 wks vs. 12 wks.). Besides that, 94% of our participants' ALT values were in the clinical range (<35 U/L) which indicated normal liver health. Although ALT was not significantly altered post-intervention, 50% of the participants in the HIIT Group presented superior ALT value, relative to baseline.

5. LIMITATIONS IN THIS STUDY

This study was not free from limitations. Immune system parameters, such as immune cell function was not studied. Hence, this did not warrant a related mechanism regarding the positive effects of HIIT on metabolism of xenobiotics and PFT. Future studies should include that parameter to provide essential data and more applicable conclusions. Secondly, an improvement

in liver function was not evident. In this sense, aspartate aminotransferase, total protein, or other liver function parameters such as alpha-fetoprotein, total bilirubin, or gamma-glutamyl transferase should be investigated along with ALT to precisely interpret changes in liver function.

6. CONCLUSIONS

Based on the findings of this study, HIIT enhances Lungs function including metabolism of xenobiotics and PFT in individuals post-COVID-19 infection. This knowledge might bring relevant contributions to this research area and clinical practice. That is, HIIT can be applied as part of the broader prevention and rehabilitation regimens of COVID-19 by health professionals.

7. STUDY PROTOCOLS

Eighty participants passed screening and were subsequently randomized into 2 Groups: (a) the Control Group (n = 40); and (b) the HIIT Group (n = 40). The participants were allocated to each group according to the participation sequence. Namely, the participants with odd numbers were assigned to the Control Group and the participants with even numbers were assigned to the HIIT Group. The participants in each Group were assigned to the experimental program that lasted 8 weeks. Prior to and following the program Lungs function was determined, including metabolism of xenobiotics concentration, estimated endogenous hormones rate and Pulmonary Function Test (PFT), and liver function including serum alanine aminotransferase (ALT) concentration.

8. ETHICS STATEMENT

All the participants were informed of information regarding the study protocols, risks, and potential benefits of participation in the study. Subsequently, each participant signed a written informed consent before screening. The consent form and the study protocols were in accordance with the ethical standards of the Human Ethics Committee of Madhv University Sirohi.

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