Suez Canal University Medical Journal Vol. 26 (10), 2023
Pages 54-66

Pulmonary Hypertension and Functional Impairment in Exercise Capacity 3 Months after Recovery from COVID-19 Infection

Fathy A. Nada[1*], Mohamed Sabry[2], Fathi Maklady[1], Ahmed Tageldein[1]

[1]*Department of Cardiovascular Medicine, Faculty of Medicine, Suez Canal University, Egypt.*
[2]*Department of Cardiovascular Medicine, Faculty of Medicine, Zagazig University, Elahrar Hospital, Egypt.*

Abstract

***Background*: COVID-19 infection can lead to significant cardiovascular complications, including pulmonary hypertension (PH) and functional impairment. This study investigates the prevalence and functional impairment in non-critical, non-mechanically ventilated patients three months post-recovery from COVID-19 at Suez Canal University Hospital in Ismailia City. *Methods*: Conducted as a cross-sectional descriptive study, it included 104 non-critically ill patients three months after recovering from COVID-19 pneumonia. Participants were categorized into mild and moderate/severe groups based on WHO criteria. We measured troponin and CRP levels at admission, performed echocardiographic assessments of the right ventricle, calculated pulmonary artery systolic pressure, and conducted a six-minute walk test to evaluate functional status. *Results*: Pulmonary hypertension was found in 72% of patients, with a higher prevalence in the moderate/severe group. Additionally, functional capacity impairment was more pronounced in this group. A significant negative correlation was observed between troponin I levels (r = -0.808), CRP levels (r = -0.681), pulmonary hypertension (r = -0.930), and functional status. *Conclusions:* PH is common in non-critical COVID-19 cases, affecting 72% of patients. There is a significant negative correlation between baseline troponin I and CRP levels, pulmonary hypertension, and functional impairment.**

Keywords: COVID-19- Pulmonary Hypertension- Six-minute Walk test

Introduction

The coronavirus disease-19 (COVID-19), initially identified in Wuhan, China, and subsequently declared a pandemic, has resulted in significant morbidity and mortality on a global scale [(1)]. On February 14, 2020, Egypt reported its initial case of COVID-19 infection. The COVID-19 virus has the potential to transmit via airborne droplets and microscopic particles. Individuals may remain infectious for as long as 20 days and can transmit the disease even in the absence of symptoms [(2)]. The COVID-19 epidemic has presented substantial limitations to healthcare systems worldwide [(3)]. Recent research advancements on severe acute respiratory syndrome coronavirus 2 (SARS-

*Corresponding Author: Fathynada45@hotmail.com,

CoV-2) have demonstrated that the virus has a profound impact on cardiac tissues, affecting their structure and function significantly [4]. It is possible for patients who have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to exhibit a wide range of symptoms, which may range from having no symptoms at all to suffering severe illness. According to the severity of the disease, which will be addressed in further depth in the methodology, individuals who have SARS-CoV-2 infection may be categorized as having mild, moderate, severe, or critical sickness. In general, this classification is based on the severity of the disease [5]. There is a possibility that some individuals may continue to have symptoms after recovering from SARS-CoV-2 infection. These symptoms are referred to as post-COVID-19 syndrome or protracted COVID-19. Based on the findings of studies, around sixty percent of patients may have at least one of these symptoms, which may last for weeks or even months. Shortness of breath, fatigue, cough, muscular discomfort, and overall weakness (asthenia) are the most typical symptoms that patients experience after COVID-19. These symptoms may have a considerable influence on a patient's ability to carry out their regular activities [6, 7]. Due to the limitations of cardiorespiratory fitness and pulmonary function that are the results of COVID-19, it is conceivable for a person to have persistent fatigue and weakness. This is a possibility [8]. This has led to a piqued interest in the field of medical research to examine the cardiorespiratory response and functional capacity of patients who have recovered from COVID-19. The objective of this investigation is to create a rehabilitation program that has the potential to mitigate the effects of COVID-19 on the daily activities of patients [8]. There are multiple approaches to assess the functional capacity and physical performance of individuals with pulmonary deficiencies. Among these, the six-minute walk distance (6MWT) test has become the gold standard for measuring submaximal exercise capacity. It is a simple, non-invasive, and cost-effective method commonly used in both surgical and medical facilities to evaluate a patient's ability to perform everyday activities. By assessing the distance a patient can walk over six minutes, the test provides insights into their overall functional status and quality of life. This test is particularly valuable because it reflects the physical endurance required for daily tasks, making it highly relevant for patients with respiratory or cardiovascular limitations. The American Thoracic Society (ATS) introduced and standardized the 6MWT in 2002 [9], establishing clear guidelines for its implementation and interpretation. These guidelines ensure consistency and reliability in its use across different clinical settings. The test has proven to be especially effective in diagnosing and monitoring chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD) [10,11]. Research has consistently demonstrated its strong validity and reproducibility in assessing exercise capacity and tracking disease progression, making it an indispensable tool in the management of pulmonary and cardiac diseases. The objective of our study is to assess the prevalence of pulmonary complications and the extent of functional impairment in non-critical, non-mechanically ventilated patients three months after recovering from COVID-19. This research was conducted at Suez Canal University Hospital in Ismailia City.

Subjects and Methods

A cross-sectional study was performed on

the population of Ismailia City with approval from the Research Ethics Committee of Suez Canal University. The research was performed on the population members. The exclusion and inclusion criteria were used to select eligible individuals, and two groups were established. The post-COVID-19 patients were divided into mild and moderate/severe categories, with critically ailing patients being excluded from the study. Patients who are adults and have been infected with SARS-CoV-2 may be divided into the following categories according to the severity of their illness [5]:

- Mild illness: Individuals exhibiting any of the following COVID-19 symptoms and signs (e.g., fever, sore throat, cough, headache, malaise, myalgia, vomiting, nausea, diarrhea, anosmia, ageusia) without dyspnea or abnormal chest imaging, and who do not need hospitalization.
- Moderate illness: Individuals with lower respiratory tract illness confirmed through clinical or radiological evaluation and requiring hospitalization are classified as having an oxygen saturation (SpO2) of 94% or higher, as measured by pulse oximetry performed on ambient air at sea level.
- Severe illness: individuals who have a respiratory rate that is more than thirty breaths per minute, a PaO2/FiO2 ratio that is less than 300 mm Hg, a SpO2 level that is lower than 94% on room air at sea level, or lung infiltrates that are greater than fifty percent, which requires them to be admitted to a ward.
- Critically sick patients: those patients who have severe respiratory failure and need mechanical ventilation and hospitalization in the critical care unit throughout their treatment.

Inclusion Criteria

- Patients who have received a positive diagnosis for COVID-19 by a polymerase chain reaction (PCR) test validated by a physician.
- Three months after the commencement of acute sickness (post-recovery period).
- Mild, moderate, and severe COVID-19 symptoms according to WHO standards, excluding critically sick and mechanically ventilated patients.
- Subjects who are age-matched (over 18) and gender-matched.

Exclusion Criteria

- Subjects had a history of respiratory or cardiac diseases, including asthma, acute myocardial infarction, and tuberculosis.
- History of musculoskeletal diseases that hinder the execution of the test, including recent fractures or advanced osteoarthritis.
- History of recurrent hemoptysis.
- Tobacco use, Obesity, neoplasia, and inadequately controlled diabetes mellitus.
- Subjects unable to finish the examination owing to causes such as neuromuscular disorders or mental illness
- Subjects undergoing oxygen treatment.
- Subjects using orthoses or prostheses.
- Subjects exhibiting exacerbated symptoms during data collecting.

A structured questionnaire was used to collect the patient's basic clinical data, and an examination was done on all patients enrolled in the study, including general and local cardiac examinations. Resting 12 lead

ECG and echocardiography were performed on all patients. Echocardiography was performed (General Electric Healthcare Company, Vivid iq) with a 2.5-MHz phased array probe. An evaluation of chamber dimensions and functionality, valvular pathology, and the probability of pulmonary hypertension was conducted. Measurements were performed retrospectively and offline using historical photographs by two independent observers who were unaware of the clinical data. The severity of tricuspid regurgitation was evaluated via color flow from the apical four-chamber perspective. The inferior vena cava (IVC) was seen in the subcostal view, and its diameter was evaluated [12,13]. A continuous-wave (CW) Doppler was used on the television to determine the right ventricular systolic pressure (RVSP) after including the predicted right atrial pressure based on the dimensions and collapsibility of the inferior vena cava (IVC) [14,15]. The estimation of Pulmonary Artery Systolic Pressure (PASP) was conducted using the following formula: SPAP = 4 times (tricuspid regurgitation (TR) peak velocity)^2 + right atrial pressure (RAP);[16]Pulmonary hypertension (PH) is characterized by a systolic pulmonary artery pressure (SPAP) over 35 mm Hg, with severity classified as mild (35–44 mm Hg), moderate (45–60 mm Hg), and severe (>60 mm Hg) [17,18]. The assessment of RAP (central venous pressure) and TR grading was conducted in accordance with established recommendations [16].

Six-Minute Walk Test

The following procedures were done following ATS guidelines to determine the selected patients' exercise capacity and functional impairment [9]. Before initiating the test, each subject's demographic information was collected and recorded. Using a pulse oximeter, the following parameters were measured: heart rate (HR), respiratory rate (RR), blood pressure (BP), and oxygen saturation (SpO_2). It was taught to the participants that they should walk as far as they could in six minutes. Every minute, participants were given standardized instructions, and they were permitted to take a break if they felt as if they were out of breath. They were then allowed to resume walking when they were ready to do so. The participant's score on the test was determined by the distance that they were able to traverse. Two examinations were carried out, with a break interval of twenty to thirty minutes in between each one, to aid learning and increase performance.

Statistical Analysis

The statistical analysis was conducted using R software, version 4.2.1. A p-value of <0.05 was set as the threshold for determining statistical significance. Quantitative variables were summarized using means and standard deviations, while categorical variables were described using absolute numbers and percentages. To assess differences before and after the tests, paired t-tests were employed for variables such as respiratory rate (RR), heart rate (HR), blood pressure (BP), and oxygen saturation (SpO2). Independent t-tests were utilized to compare group means, and categorical variables were analyzed using Chi-square tests. The results of the 6-Minute Walk Test (6MWT), specifically the total distance walked, were examined for bivariate correlations using Pearson's correlation coefficient. Also, scatter plots with regression lines were generated to assess the relationships between variables.

Results

A total of 207 people were originally en

rolled in the study; however, 103 patients diagnosed with COVID-19 were not included for various reasons, as seen in Figure 1. After completing all of the tests, a total of 104 people were examined for the research. These subjects were separated into two groups: fifty patients went into the mild group, and fifty-four patients went into the moderate/severe group.

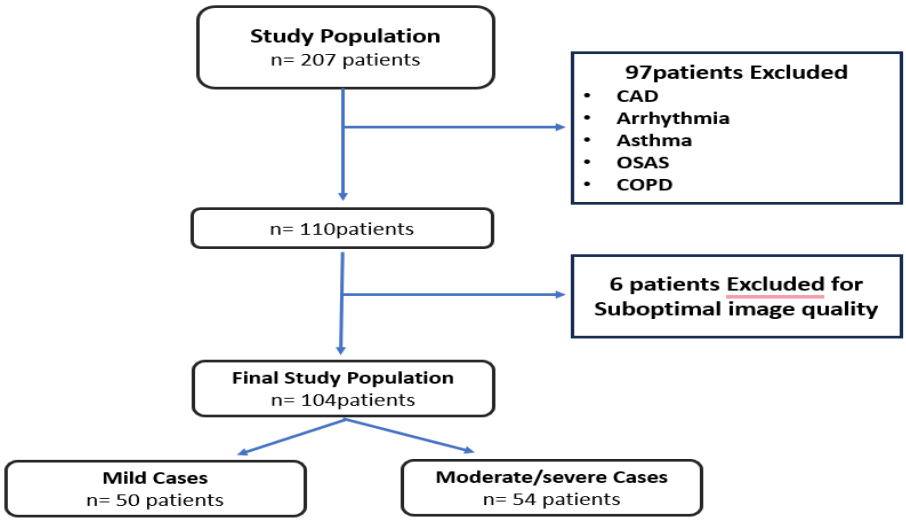

Figure: The study population selected

A total of thirty-three healthy controls were matched. It was found that the mean age was 48.8 years with a standard deviation of 10.7 years, with the majority of the participants being male (55.8 percent). As shown in Table 2, seventy-five patients in the study developed pulmonary hypertension 3 months after recovery from the COVID infection representing 72% of the studied population. Sixty percent of the mild group while 83.3% of the mild to severe group developed pulmonary hypertension. As demonstrated in Table 1, there is a statistically significant difference between the group who developed pulmonary hypertension and those without regarding Troponin level at baseline admission indicating myocardial injury and CRP at baseline admission indicating the role of inflammatory response. Table 2 highlights a comparison between functional capacity and post-test cardiorespiratory responses among patients classified as mild and those categorized as moderate/severe. Regarding functional capacity, measured by the 6-minute walk test (6MWT), the mild group walked an average of 510.14 ± 43.14 meters, while the moderate/severe group covered 414.65 ± 56.29 meters. This indicates a significant mean difference of 95.45 ± 13.15 meters ($p < 0.001$), reflecting better functional capacity in the mild group. Regarding the post-test heart rate, the mild group had an average of 101 ± 11 beats per minute compared to 108 ± 7 beats per minute in the moderate/severe group, with a statistically significant difference of 7 ± 4 beats per minute ($p = 0.041$). The post-test respiratory rate also showed a notable increase in the moderate/severe group (27.6 ± 2.3 breaths/min) compared to the mild group (23 ± 3 breaths/min), with a significant mean difference of 4.6 ± 0.7 breaths/min ($p<0.001$). While the mild group exhibited slightly higher post-test oxygen saturation (SpO_2) levels (98.1 ±

0.3%) compared to the moderate/severe group (97.9 ± 0.2%), the difference of 0.2 ± 0.10% was not statistically significant (p=0.243). Similarly, differences in post-test systolic blood pressure (128.7 ± 8.2 mmHg vs. 129.4 ± 3.2 mmHg, p=0.741) and diastolic blood pressure (78.8 ± 3.7 mmHg vs. 82.4 ± 3.1 mmHg, p=0.312) were not significant. These findings suggest that while functional capacity and some post-test parameters, such as heart and respiratory rates, differed significantly, others like SpO2 and blood pressure showed no significant variation between the groups. As shown in Table 3 and Figure 3 there is a statistically substantial strong negative correlation between the PASP level and the walking distance in the 6MWT (r=0.930). The more the PASP, the less the distance walked in the 6MWT. Table 4: Spearman's correlation coefficient for the relation between CRP levels at admission and 6MWD among study participants (n=104).

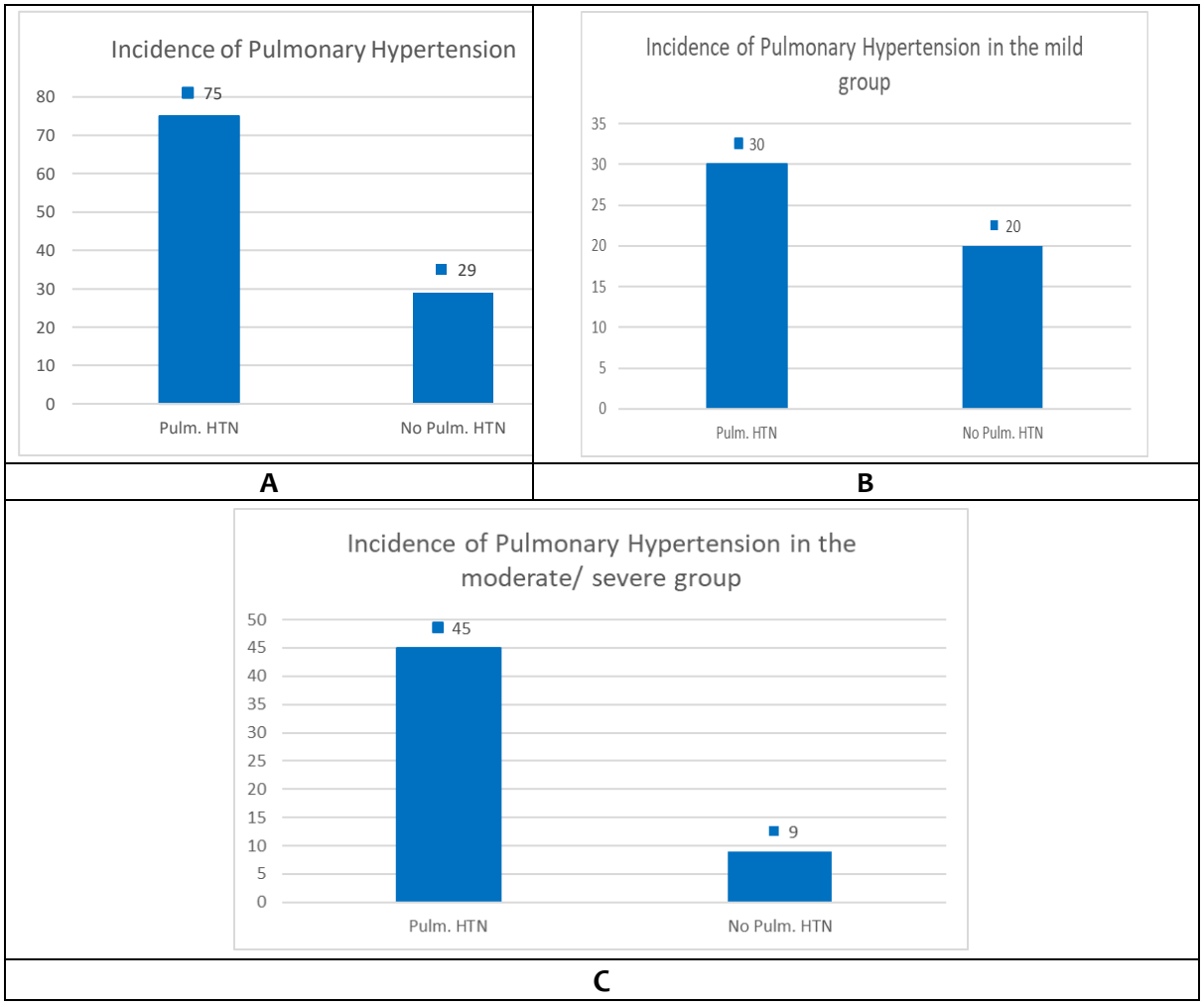

Figure 2: Development of Pulmonary hypertension in the studied population. (A) in all population included. (B) in the mild group only. (C) in the moderate/ severe group only.

As shown in Table 4 and Figure 4 there is a statistically significant moderate negative correlation between the CRP level at admission and the walking distance in the

6MWT (r=-0.861). The higher the CRP level at admission, the less the distance walked in the 6MWT. As shown in Table 5 and Figure 5 there is a statistically significant neg

ative correlation between the CRP level at admission and the walking distance in the 6MWT (r=-0.861). The higher the troponin level at admission, the less the distance walked in the 6MWT.

Table 1. The distinction between patients with pulmonary hypertension and those without in terms of troponin, CRP, and 6MWD.

Lab test	No pulmonary HTN (n = 29)	Pulmonary HTN (n = 75)	*p*-value
Troponin (mean ± SD)	19.6 ± 24.7	39.2 ± 27.5	**< 0.001**[1*]
CRP (mean ± SD)	12.6 ± 4.2	16.1 ± 5.4	**0.003**[1*]

1. Mann Whitney U test; *Statistically significant at $p < 0.05$.

Table 2. Comparison of functional capacity and post-cardiorespiratory responses between the two groups.

Variables	Mild Group N= (Mean ±SD)	Moderate/Severe Group N= (Mean ±SD)	Mean Difference ± SD	*p*-Value
Distance (m)	510.14 ± 43.14	414.65 ± 56.29	95.45 ± 13.15	<0.001
Post-HR	101 ± 11	108 ± 7	7± 4	0.041
Post-RR	23±3	27.6 ±2.3	4.6±0.7	<0.001
Post-Spo2	98.1±0.3	97.9±0.2	0.2±0.10	0.243
Post-Systolic BP	128.7±8.2	129.4±3.2	-0.7±0.5	0.741
Post-Diastolic BP	78.8±3.7	82.4±3.1	4.4±30.6	0.312

Discussion

This study revealed a strong association between the occurrence of pulmonary hypertension and the severity of cases. The findings indicated that 72% of the participants developed pulmonary hypertension within three months after recovering from COVID-19. Similarly, research conducted by Taha et al., published in the *Egyptian Journal of Bronchology*, reported a comparable incidence rate of 70% for pulmonary hypertension following COVID-19 recovery [19]. Research published in the *Journal of the American College of Cardiology (JACC)* reported that approximately 10-15% of individuals who recovered from mild to severe cases of COVID-19 experienced elevated pulmonary artery pressures three months post-recovery [20]. Research published by Antoniou et al., in European Respiratory Journal indicated that about 5-10% of non-hospitalized COVID-19 patients showed signs of PH during follow-up assessments [21]. A study featured in *Nature Communications* revealed that up to 20% of individuals with post-acute sequelae of SARS-CoV-2 infection (PASC), commonly referred to as long COVID-19, exhibited symptoms of pulmonary hypertension (PH). This prevalence was observed even among patients who had not been critically ill during the acute phase of the infection [22]. This high percentage in our study could be explained by the fact that our study group had delayed presentations to the healthcare system. They began receiving home and non-specific treatments on an outpatient basis.

Potential Mechanisms [23]

Persistent Lung Damage:

Fibrosis: COVID-19 can cause significant lung injury, leading to pulmonary fibrosis,

which stiffens the lung tissue leading to vascular resistance.

Inflammation: Ongoing low-grade lung inflammation can contribute to vascular changes and PH.

Endothelial Dysfunction: COVID-19 is known to cause endothelial cell damage, leading to vasoconstriction, thrombosis, and increased pulmonary vascular resistance, contributing to PH.

Table 3: Spearman's correlation coefficient for the relation between PSAP levels and 6MWD among study participants (n=104)		
	6MWD (Mean ± SD) 441.31 ± 68.19	
	r	p-value
PASP (Mean ± SD) 39.78 ± 6.58	-0.930**	< 0.001*

*Statistically significant at $p < 0.05$, **. Correlation is significant at the 0.01 level (2-tailed)

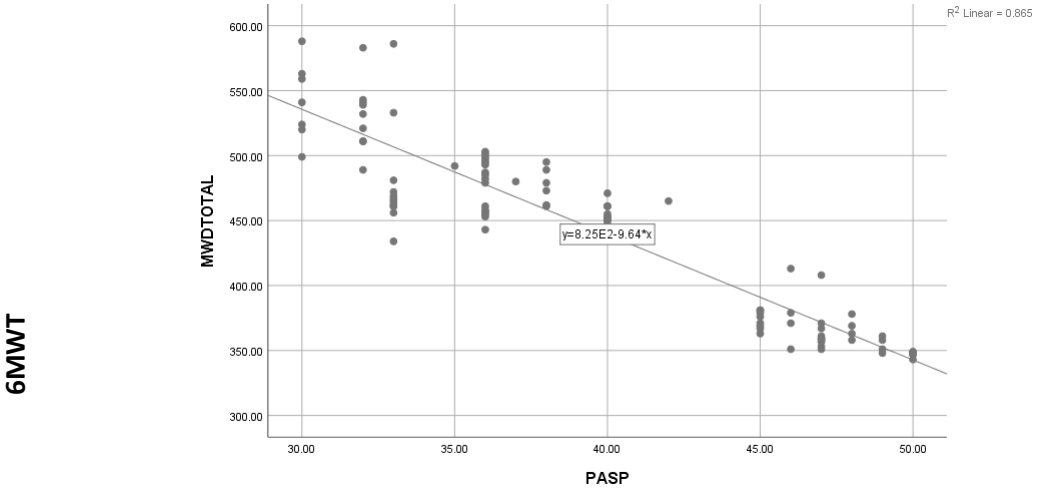

Figure 3 Scatter Plot showing the correlation between the pulmonary artery systolic pressure and the 6-minute walking distance test.

Correlation between CRP and 6MWD		
	6MWD (Mean ± SD) 441.31 ± 68.19	
	r	p-value
CRP (Mean ± SD) 15.12 ± 5.34	-0.681**	< 0.001*

*Statistically significant at p < 0.05, **. Correlation is significant at the 0.01 level (2-tailed)*

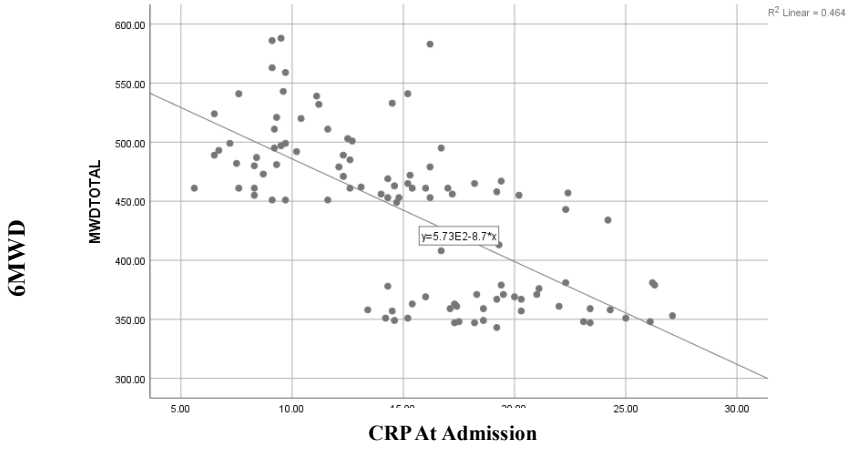

Figure 4 Scatter Plot showing the level of CRO at admission and the 6-minute walking distance test.

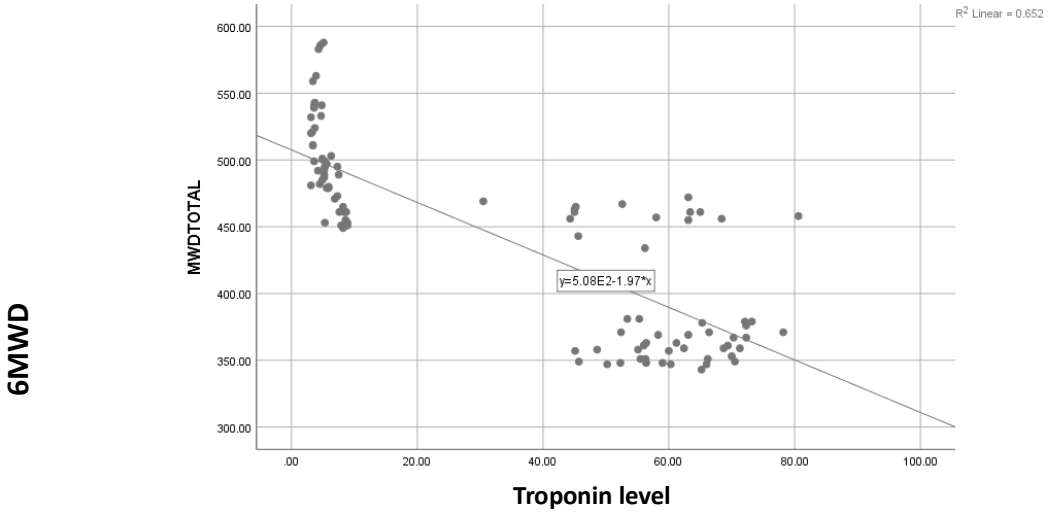

Table 4: Spearman's correlation coefficient for the relation between PSAP levels and 6 MWD among study participants (n=104)		
	6MWD (Mean ± SD) 441.31 ± 68.19	
	r	p-value
Troponin (Mean ± SD) 33.69 ± 28.02	-0.808**	< 0.001*

**Statistically significant at p < 0.05, **. Correlation is significant at the 0.01 level (2-tailed)*

Microthrombi and Vascular Occlusion: The formation of microthrombi in pulmonary vessels during the acute phase of COVID-19 can persist and lead to chronic thromboembolic pulmonary hypertension (CTEPH). **Hypoxia-Induced Pulmonary Vasoconstriction:** Chronic hypoxia, resulting from persistent lung damage and impaired gas exchange, can cause vasoconstriction and contribute to the development of PH [23]. Our study showed that individuals recovering from COVID-19 in the moderate/severe group have lower physical abilities compared to those in the mild group. Research published in journals like *Chest* and *European Respiratory Journal* has shown that many COVID-19 survivors have a reduced 6MWD even months after recovery. A decrease of 20-30% in the 6MWD compared to baseline values has been reported in some cohorts [24] Data from post-COVID-19 clinics indicate that up to 40-60% of patients evaluated 3-6 months post-infection exhibit a reduced 6MWD, highlighting persistent functional impairment [25]. The six-minute step test, often referred to as the 6MST, conducted on individuals with severe COVID-19 produced results similar to those shown in earlier studies. Research conducted by Lydia J. and colleagues revealed a decrease in the average number of steps climbed, recorded at 86 ± 39 steps [26]. Furthermore, research conducted by Bianca Setra and associates revealed subpar performance on the 6MST, with individuals averaging 92.3 ascending steps [27]. The reduced performance observed in the post-COVID-19 group may be attributed to a combination of intrapulmonary and extrapulmonary factors. Intrapulmonary causes include pathological changes in the lung tissue caused by the SARS-CoV-2 virus, which can lead to structural and functional impairments. These alterations often result in pulmonary dysfunction and abnormalities in gas exchange, further compromising respiratory efficiency and physical performance [28]. Studies have shown that

individuals who have been exposed to COVID-19 often have problems in pulmonary function, decreased diffusion capacity, pulmonary vascular damage, and weak respiratory muscles [29, 31]. The inflammatory response that is caused by the virus may be connected with extrapulmonary reasons such as arthralgia, myalgia, and paralysis. These abnormalities in the neuromuscular system are related with the virus [32]. Modified lung function, sarcopenia, and chronic inflammation are some of the factors that might make it difficult to exercise following COVID-19 [33]. A decline in performance in the post-COVID-19 group may also be caused by factors such as inactivity during the quarantine period or the effects of their medication [33]. The Post-COVID Functional Scale (PCFS) reveals that persons who underwent COVID-19 encountered very little impairments in their day-to-day activities. This percentage accounts for 55% of the total. There was a connection between these limits and weariness as well as trouble breathing [34]. The post-COVID-19 group did not experience any oxygen desaturation throughout the testing process, despite the fact that they did experience weariness and moderate dyspnea. Patients who have recovered from COVID-19 may have fatigue and dyspnea as a result of immunological reactions that cause lingering lung abnormalities or psychological discomfort brought on by conditions such as anxiety, sleeplessness, and depression [34, 35]. According to the findings of a research conducted by Sperling and colleagues, tiredness is a symptom that is often and persistently experienced by younger COVID-19 patients who have normal PFT. In addition, they noted that desaturation during exercise was only seen in instances that were severe after COVID-19 had been administered. Post-COVID-19 individuals may have prolonged tiredness and shortness of breath as a consequence of an immunological reaction to ACE2, which causes residual damage and alterations in the lungs. This, in turn, causes patients to experience fatigue and shortness of breath [37]. In addition, individuals who are diagnosed with COVID-19 often report psychological discomfort, which may include symptoms such as anxiety, sleeplessness, and depression. These symptoms may be contributing causes. A correlation between exhaustion and anxiety has been established via research, which was not previously recognized in the participants before the COVID-19 study. Furthermore, Hugo B and colleagues came to the conclusion that anxiety and sadness after COVID-19 episodes are associated with an increased likelihood of suffering from persistent symptoms such as pain and dyspnea [38].

Conclusion

This study indicates that 72 percent of subjects had pulmonary hypertension three months post-recovery from a Covid-19 infection. A reduced 6MWD was often seen among these individuals, indicating a functional impairment in exercise capacity. This was seen even among cohorts of patients who were not in serious condition. This impairment was shown to correlate with the severity of the first presentation, which was previously unrecognized. The 6MWD, when used as an assessment instrument for COVID-19 patients, may aid in evaluating their functional capacity and daily activities.

Limitations

A small number of patients on whom the study was conducted. Diagnosis of pulmonary hypertension in this study depends on transthoracic echocardiography instead of right heart catheterization.

References

1. Khalid M, Awan S, Jatoi NN, et al.: Cardiac manifestations of the coronavirus disease-19: a review of pathogenesis, clinical manifestations, diagnosis, and treatment. Pan Afr Med J 2021, 39.
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020, 55:105924.
3. Li YC, Syed-Abdul S, Filip R, et al.: Personalized Medicine Review Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. 2022, doi:10.3390/jpm12081295.
4. Dhakal BP, Sweitzer NK, Indik JH, Acharya D, William P: SARS-CoV-2 Infection and Cardiovascular Disease: COVID-19 Heart. Heart Lung Circ 2020, 29:973.
5. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R: Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls 2023,
6. Malkova A, Kudryavtsev I, Starshinova A, et al.: Post COVID-19 Syndrome in Patients with Asymptomatic/Mild Form. Pathogens 2021, 10.
7. So MKP, Chu AMY, Tiwari A: Persistent symptoms after SARS-CoV-2 infection: Long-term implications for health and quality of life. The Lancet Regional Health - Europe 2022, 17.
8. Schwendinger F, Knaier R, Radtke T, Schmidt-Trucksäss A: Low Cardiorespiratory Fitness Post-COVID-19: A Narrative Review. Sports Med 2023, 53:51.
9. Crapo RO, Casaburi R, Coates AL, et al.: ATS Statement. https://doi.org/101164/ajrccm1661.at1102 2012, 166:111–117.
10. Hernandes NA, Wouters EFM, Meijer K, et al.: Reproducibility of 6-minute walking test in patients with COPD. European Respiratory Journal 2011, 38:261–267.
11. Hansen H, Beyer N, Frølich A, Godtfredsen N, Bieler T: Intra- and inter-rater reproducibility of the 6-minute walk test and the 30-second sit-to-stand test in patients with severe and very severe COPD. Int J Chron Obstruct Pulmon Dis 2018, 13:3447.
12. Rudski LG, Lai WW, Afilalo J, et al.: Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. Journal of the American Society of Echocardiography 2010, 23:685–713.
13. Zaidi A, Knight DS, Augustine DX, et al.: Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. Echo Res Pract 2020, 7:G19.
14. Ghidini S, Gasperetti A, Winterton D, et al.: Echocardiographic assessment of the right ventricle in COVID-19: a systematic review. Int J Cardiovasc Imaging 2021, 37:3499–3512.
15. D'Andrea A, Scarafile R, Riegler L, et al.: Right Ventricular Function and Pulmonary Pressures as Independent Predictors of Survival in Patients With COVID-19 Pneumonia. JACC Cardiovasc Imaging 2020, 13:2467–2468.
16. Bossone E, D'Andrea A, D'Alto M, et al.: Echocardiography in Pulmonary Arterial Hypertension: from Diagnosis to Prognosis. Journal of the American Society of Echocardiography 2013, 26:1–14.
17. Douglas PS, Carabello BA, Lang RM, et al.: 2019 ACC/AHA/ASE key data ele-

ments and definitions for transthoracic echocardiography: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Transthoracic Echocardiography) and the American Society of Echocardiography. Circ Cardiovasc Imaging 2019, 12:27.

18. Bursi F, Santangelo G, Sansalone D, et al.: Prognostic utility of quantitative offline 2D-echocardiography in hospitalized patients with COVID-19 disease. Echocardiography 2020, 37:2029–2039.
19. Abdelhady Taha H, Elshafey I, Abdullah TM, Salem HA: RESEARCH Open Access Study of pulmonary hypertension in post-COVID-19 patients by transthoracic echocardiography. The Egyptian Journal of Bronchology 2023, 17:27.
20. Bozkurt B, Das SR, Addison D, et al.: 2022 AHA/ACC Key Data Elements and Definitions for Cardiovascular and Noncardiovascular Complications of COVID-19: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. Circ Cardiovasc Qual Outcomes 2022, 15:E000111.
21. Antoniou KM, Vasarmidi E, Russell AM, et al.: European Respiratory Society statement on long COVID follow-up. European Respiratory Journal 2022, 60.
22. Krueger T, Van Den Heuvel J, Van Kampen-Van Den Boogaart V, et al.: Pulmonary function three to five months after hospital discharge for COVID-19: a single centre cohort study. 123AD, doi:10.1038/s41598-023-27879-8.
23. Saifi MA, Bansod S, Godugu C: COVID-19 and fibrosis: Mechanisms, clinical relevance, and future perspectives. Drug Discov Today 2022, 27:103345.
24. Kattainen S, Lindahl A, Vasankari T, et al.: Lung function and exercise capacity 6 months after hospital discharge for critical COVID-19. BMC Pulm Med 2022, 22:1–10.
25. Assiri AM, Alamaa T, Elenezi F, et al.: Unveiling the Clinical Spectrum of Post-COVID-19 Conditions: Assessment and Recommended Strategies. Cureus 2024, doi:10.7759/CUREUS.52827.
26. Finney LJ, Doughty R, Lovage S, et al.: Lung function deficits and symptom burden in survivors of COVID-19 requiring mechanical ventilation. Ann Am Thorac Soc 2021, 18:1740–1743.
27. Kovalski BS, Gonçalves Vergel L, Dió-rio F, et al.: Physical capacity assessment in patients hospitalized with COVID-19 diagnose. Fisioterapia e Pesquisa 2022, 29:216–222.
28. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, et al.: Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology 2021, 27:328.
29. Mo X, Jian W, Su Z, et al.: Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020, 55.
30. Huang Y, Tan C, Wu J, et al.: Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res 2020, 21:163.
31. Chen R, Gao Y, Chen M, et al.: Impaired pulmonary function in discharged patients with COVID-19: more work ahead. Eur Respir J 2020, 56.
32. Hasan LK, Deadwiler B, Haratian A, et al.: Effects of COVID-19 on the Musculoskeletal System: Clinician’s Guide . Orthop Res Rev 2021, 13:141–150.
33. Ribeiro Baptista B, d'Humières T, Schlemmer F, et al.: Identification of factors impairing exercise capacity after severe COVID-19 pulmonary infec-

tion: a 3-month follow-up of prospective COVulnerability cohort. Respir Res 2022, 23.
34. Fernández-De-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al.: Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. Respiration 2022, 101:132–141.
35. Wensink M, Schaap G, ten Klooster PM, et al.: Physical and mental fatigue in post-COVID syndrome and their associations over time: A small-sample ESM-study to explore fatigue, quality of sleep and behaviors. J Psychosom Res 2023, 164:111084.
36. Sperling S, Fløe A, Leth S, et al.: Fatigue Is a Major Symptom at COVID-19 Hospitalization Follow-Up. J Clin Med 2022, 11:2411.
37. Townsend A: Autoimmunity to ACE2 as a possible cause of tissue inflammation in Covid-19. Med Hypotheses 2020, 144:110043.
38. Bottemanne H, Gouraud C, Hulot JS, et al.: Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study. Front Psychiatry 2021, 12:757685.