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# Powikłania i wpływ COVID-19 na funkcję mięśnia sercowego i wydolność wysiłkową

Complications and impact of COVID-19 on myocardial function and exercise capacity

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Promotor

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## 2. WYKAZ STOSOWANYCH SKRÓTÓW I SŁOWA KLUCZOWE

1. **A** (*ang. late diastolic filling velocity*) – maksymalna prędkość fali przedsionkowej
2. **AA** *(ang. ascending aorta)* – aorta wstępująca
3. **AB** *(ang. aortic bulb)* – opuszka aorty
4. **ACE2** (*ang. angiotensin-converting enzyme 2*) – enzym konwertujący angiotensynę 2
5. **ASE** *(ang. American Society of Echocardiography)* – Amerykańskie Towarzystwo Echokardiograficzne
6. **Ats** *(ang. acceleration time)* – czas akceleracji
7. **AUC** (*ang. area under the curve*) – pole pod krzywą
8. **BIA** *(ang. bioelectrical impedance analysis)* – analiza metodą bioimpedancji elektrycznej
9. **CI** (*ang. confidence interval*) – przedział ufności
10. **COVID-19** (*ang. Coronavirus Disease 2019*) - choroba zakaźna wywoływana przez drugi koronawirus ciężkiego ostrego zespołu oddechowego
11. **CPET** (*ang. cardiopulmonary exercise testing*) – sercowo-płucny test wysiłkowy
12. **Dec** *(ang. deceleration time)* – czas deceleracji
13. **DLCO** *(ang. diffusing capacity of the lungs for carbon monoxide)* – zdolność dyfuzyjna płuc dla tlenku węgla
14. **DXA** *(ang. dual enerdy X-ray absorptiometry)* – absorpcjometria rentgenowska o podwójnej energii
15. **E** (*ang. early diastolic filling velocity*) - maksymalna prędkość wczesnego napływu mitralnego
16. **E'** (*ang. early diastolic mitral annular velocity*) – wczesnorozkurczowa prędkość pierścienia mitralnego
17. **EAE** *(ang. European Association of Echocardiography)* – Europejskie Towarzystwo Echokardiograficzne
18. **E/A** (*ang. ratio of early to late ventricular filling velocities*) - stosunek fali E do fali A
19. **E/E'** (*ang. ratio of early diastolic filling velocity to early diastolic mitral annular velocity*) - stosunek fali E do fali E'
20. **ECW** *(ang. extracellular water)* – woda zewnątrzkomórkowa
21. **ECW/TBW% -** stosunek ECW do TBW
22. **EDTA** *(ang. ethylenediaminetetraacetic acid)* – kwas etylenodiaminotetraoctowy

23. **EDV** (*ang. end-diastolic volume*) - objętość końcoworozkurczowa lewej komory
24. **ELISA** *(ang. enzyme-linked immunosorbent assay)* – test immunoenzymatyczny
25. **ESV** (*ang. end-systolic volume*) - objętość końcowoskurczowa lewej komory
26. **FEV1** (*ang. forced expiratory volume in 1 second*) - natężona objętość wydechowa pierwszosekundowa
27. **FEV1/FVC%** (*ang. Tiffeneau index*) – wskaźnik Tiffeneau (procentowy stosunek FEV1 do FVC)
28. **FFM** *(ang. fat free mass)* – beztłuszczowa masa ciała
29. **FM** *(ang. fat mass)* – zawartość tkanki tłuszczowej
30. **FVC** (*ang. forced vital capacity*) - natężona pojemność życiowa
31. **GFR** (*ang. glomerular filtration rate*) - współczynnik filtracji kłębuszkowej
32. **GLPS** (*ang. global longitudinal peak systolic strain*) - globalne podłużne szczytowe odkształcenie skurczowe lewej komory
33. **HBV** (*ang. Hepatitis B Virus*) - wirus zapalenia wątroby typu B
34. **HCV** (*ang. Hepatitis C Virus*) - wirus zapalenia wątroby typu C
35. **HF** (*ang. heart failure*) - niewydolność serca
36. **HIV** (*ang. Human Immunodeficiency Virus*) - ludzki wirus niedoboru odporności
37. **HR** *(ang. heart rate)* – częstotliwość rytmu serca
38. **Hs-cTnT** (*ang. high-sensitivity cardiac troponin T*) – wysokoczuła troponina T
39. **ICW** *(ang. intracellular water)* - woda wewnątrzkomórkowa
40. **IQR** (*ang. interquartile range*) - rozstęp międzykwartylowy
41. **IVC** *(ang. inferior vena cava)* - żyła główna dolna
42. **IVS** *(ang. interventricular septum)* – wymiar przegrody międzykomorowej
43. **LA** (*ang. left atrium*) - lewy przedsionek
44. **LAV** *(ang. left atrial volume)* – objętość lewego przedsionka
45. **LAVI** *(ang. left atrial volume indeks)* – indeksowana objętość lewego przedsionka
46. **LVEF** *(ang. left ventricular ejection fraction)* – frakcja wyrzutowa lewej komory
47. **LVID** *(ang. left ventricular internal diameter)* – wymiar końcoworozkurczowy lewej komory
48. **LVMI** (*ang. left ventricular mass index*) – indeks masy lewej komory
49. **LVPW** *(ang. left ventricular posterior wall)* – wymiar tylnej ściany lewej komory
50. **MPA** *(ang. main pulmoray artery)* – pień płucny
51. **NKF** (*ang. National Kidney Foundation*) – Amerykańska Narodowa Fundacja Nefrologiczna

52. **OR** (*ang. odds ratio*) – iloraz szans
53. **RAA** *(ang. right atrial area)* – pole prawego przedsionka
54. **RBC** *(ang. red blood cells)* - erytrocyty
55. **RER** (*ang. respiratory exchange ratio*) - współczynnik wymiany oddechowej
56. **ROC** (*ang. receiver operating characteristic curve*) - krzywa charakterystyki operacyjnej odbiornika
57. **RV** *(ang. right ventricle)* – prawa komora
58. **RVOT** *(ang. right ventricular outflow tract)* – droga odpływu prawej komory
59. **SARS-CoV-2** (*ang. Severe Acute Respiratory Syndrome Coronavirus 2*) - koronawirus zespołu ostrej niewydolności oddechowej 2
60. **TAPSE** (*ang. tricuspid annular plane systolic excursion*) – amplituda skurczowego przemieszczenia pierścienia zastawki trójdzielnej
61. **TBW** (*ang. total body water*) – zawartość wody całkowitej w organizmie
62. **TDE** *(ang. tissue Doppler echocardiography)* – echokardiografia Dopplera tkankowego
63. **TIA** (*ang. transient ischemic attack*) - przemijający atak niedokrwienny
64. **TLC** *(ang. total lung capacity)* – całkowita pojemność płuc
65. **VE** *(ang. ventilatory exchange)* – wymiana wentylacyjna
66. **VE/$VCO_2$ slope –** nachylenie wentylacji minutowej do produkcji dwutlenku węgla
67. **$VO_2$AT** *(ang. oxygen uptake at anaerobic threshold)* – pobór tlenu na progu beztlenowym
68. **$VO_{2max}$** (*ang. maximal oxygen uptake*) - maksymalne szczytowe pochłanianie tlenu
69. **%$VO_{2pred}$** (*ang. percentage of maximal predicted oxygen consumption*) - procent przewidywanego maksymalnego zużycia tlenu
70. **WHO** (*ang. World Health Organization*) - Światowa Organizacja Zdrowia

**Słowa kluczowe:** COVID-19, long COVID, wydolność fizyczna, spiroergometria
**Keywords:** COVID-19, long COVID, exercise capacity, spiroergometry

## 3. STRESZCZENIE

### 3.1. Wstęp

COVID-19 (ang. coronavirus disease 2019 – COVID-19) to choroba zakaźna wywoływana przez drugi koronawirus ciężkiego ostrego zespołu oddechowego (ang. severe acute respiratory syndrome coronavirus 2 - SARS-CoV-2). Po raz pierwszy została wykryta w grudniu 2019 r. w Wuhan w Chinach i spowodowała globalny kryzys zdrowotny. Światowa Organizacja Zdrowia (ang. World Health Organisation - WHO) 11 marca 2020 r. ogłosiła pandemię COVID-19. Szacuje się, że infekcja dotknęła prawie 800 milionów ludzi na całym świecie i była przyczyną około 7 milionów zgonów. Jednym z najważniejszych problemów wynikających z pandemii jest zespół long COVID (zespół pokowidowy). Definiuje się go jako kontynuację lub rozwój nowych objawów zwykle 3 miesiące po pierwotnym zakażeniu SARS-CoV-2, utrzymujących się co najmniej przez 2 miesiące bez żadnej innej przyczyny. Mogą pojawić się one na nowo po początkowym wyzdrowieniu z COVID-19 lub utrzymywać się po chorobie, z czasem mogą się zmieniać lub nawracać. Typowe objawy obejmują przewlekłe zmęczenie, duszność, utratę węchu i smaku, zaburzenia funkcji poznawczych. Osoby z zespołem pokowidowym często zgłaszają również pogorszoną tolerancję wysiłku fizycznego. Sercowo-płucny test wysiłkowy (ang. cardiopulmonary exercise testing - CPET) jest ważnym badaniem mającym zastosowanie w diagnostyce przyczyn nietolerancji wysiłku. Ponadto uważany jest za złoty standard w ocenie sprawności fizycznej i interakcji układów sercowo-naczyniowego, oddechowego i metabolicznego. W związku z powyższym CPET może być wartościowym narzędziem oceny wydolności fizycznej pacjentów z zespołem long COVID.

### 3.2. Cel pracy

Celem rozprawy, na którą składają się 3 prace oryginalne i 1 praca poglądowa była ocena wpływu COVID-19 na rozwój chorób układu krążenia oraz identyfikacja czynników powodujących nietolerancję wysiłku fizycznego po przebyciu infekcji.

**Publikacja 1.**

Badanie opisane w pracy pod tytułem „***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction***”

miało na celu analizę mechanizmów wpływających na nietolerancję wysiłku fizycznego u pacjentów po przebyciu COVID-19.

**Metodyka:** Włączono 120 pacjentów, którzy przebyli COVID-19 od 3 do 6 miesięcy przed przystąpieniem do badania. Przeprowadzono badanie podmiotowe, przedmiotowe, wykonano badania: laboratoryjne, echokardiograficzne, spiroergometryczne oraz analizę składu masy ciała. Podzielono ich na dwie grupy: pacjentów, którzy osiągnęli < 80% maksymalnego przewidywanego zużycia tlenu (%$VO_{2pred}$) [n=47] i pacjentów, którzy uzyskali ≥ 80% $VO_{2pred}$ [n=73] w badaniu spiroergometrycznym.

**Wyniki:** Wykazano, że mężczyźni mają dwukrotnie większe ryzyko zmniejszonej tolerancji wysiłku fizycznego niż kobiety. Z przedstawionych analiz wynika również, że pacjenci z %$VO_{2pred}$ < 80% mieli obniżone wartości globalnego podłużnego szczytowego odkształcenia skurczowego lewej komory (ang. global longitudinal peak systolic strain - GLPS), amplitudy skurczowego przemieszczenia pierścienia zastawki trójdzielnej (ang. tricuspid annular plane systolic excursion - TAPSE) i maksymalnej prędkości fali przedsionkowej (ang. late diastolic filling velocity – A) w porównaniu do grupy, która osiągnęła %$VO_{2pred}$ ≥ 80%. Na podstawie analizy wieloczynnikowej wykazano, że fala A i płeć męska są niezależnie związane z %$VO_{2pred}$.

**Wnioski:** Mężczyźni mają dwukrotnie większe ryzyko utrzymującej się ograniczonej tolerancji wysiłku w przebiegu long COVID niż kobiety. Zmniejszone wartości fali A, TAPSE, GLPS oraz stan nawodnienia są powiązane z ograniczoną tolerancją wysiłku po przebyciu COVID-19 u pacjentów z zachowaną frakcją wyrzutową lewej komory (ang. left ventricular ejection fraction - LVEF).

**Publikacja 2.**

W kolejnym badaniu przedstawionym w publikacji "***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction***" analizowano użyteczność parametrów spiroergometrycznych u pacjentów z zespołem long COVID.

**Metodyka:** Włączono 146 ochotników (3 do 6 miesięcy po przechorowaniu COVID-19), których podzielono na grupę z objawami zespołu long COVID [n=44] oraz grupę bezobjawową [n=102]. Przeprowadzono badanie podmiotowe, przedmiotowe, wykonano

badania: laboratoryjne, echokardiograficzne, spiroergometryczne oraz analizę składu masy ciała.

**Wyniki:** Udowodniono, że pacjenci z objawami long COVID byli starsi niż grupa bezobjawowa, mieli wyższe wartości wieku metabolicznego, średnicy lewego przedsionka (ang. left atrial diameter – LA), indeksu masy lewej komory (ang. left ventricular mass index - LVMI), fali A, stosunku maksymalnej prędkości wczesnego napływu mitralnego (fala E) do wczesnorozkurczowej prędkości pierścienia mitralnego (fala E') (E/E') i niższą wartość stosunku maksymalnej prędkości wczesnego napływu mitralnego (fala E) do maksymalnej prędkości fali przedsionkowej (fala A) (E/A). W badaniu CPET pacjenci z long COVID prezentowali obniżony poziom natężonej pojemności życiowej (ang. forced vital capacity – FVC), maksymalnego szczytowego pochłaniania tlenu ($VO_{2max}$), współczynnika wymiany oddechowej (ang. respiratory exchange ratio – RER), natężonej objętości wydechowej pierwszosekundowej (ang. forced expiratory volume in one second - FEV1) oraz wyższego wskaźnika Tiffeneau (FEV1/FVC%). Badania laboratoryjne wykazały zmniejszoną liczbę erytrocytów, zwiększony poziom glikemii na czczo i wysokoczułej troponiny T (ang. high-sensitivity cardiac troponin T - hs-cTnT) oraz obniżony wskaźnik filtracji kłębuszkowej (ang. glomerular filtration rate - GFR) u pacjentów z long COVID. W analizie wieloczynnikowej wykazano, że tylko FEV1/FVC% jest niezależnym czynnikiem wpływającym na pojawienie się objawów zespołu long COVID. Przy użyciu krzywej ROC (ang. receiver operating characteristic curve) udowodniono, że wartość FEV1/FVC% $\geq$ 103 jest najbardziej przydatnym parametrem CPET (0.67 czułości, 0.71 swoistości, $p < 0.001$) w przewidywaniu objawów long COVID.

**Wnioski:** Parametry spiroergometryczne są przydatne w diagnostyce zespołu long COVID oraz różnicowaniu go z chorobami układu krążenia.

**Publikacja 3.**

Ostatnia analiza opisana w artykule "***Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery***" stanowi kontynuację opisanego powyżej badania. Celem niniejszej pracy była ocena mechanizmów przyczyniających się do ograniczenia tolerancji wysiłku u ozdrowieńców COVID-19 po rocznej obserwacji.

**Metodyka:** Spośród 146 pacjentów włączonych do badania opisanego w publikacji 3., 82 z nich ukończyło roczny follow-up. Przeprowadzono takie samo postępowanie diagnostyczne jak podczas pierwszego badania. Poddano analizie zmiany parametrów laboratoryjnych, echokardiograficznych, spiroergometrycznych i analizy składu ciała po rocznej obserwacji.

**Wyniki:** Chorzy po roku prezentowali wyższe wartości hs-cTnT, LA, RER oraz procentowej zawartości wody całkowitej (ang. total body water content percentage - TBW%) w porównaniu do poprzedniej analizy. Ponadto mieli niższą wartość FVC. Zawartość tłuszczu (ang. fat mass – FM), objętość późno-rozkurczowa (ang. end-diastolic volume – EDV) i późno-skurczowa (ang. end-systolic volume – ESV) lewej komory były niezależnie powiązane ze spadkiem maksymalnego pochłaniania tlenu po rocznym follow-up.

**Wnioski:** Na podstawie przeprowadzonego badania udowodniono, że zwiększone objętości lewej komory (EDV i ESV) oraz zawartość tłuszczu (FM) wiążą się z redukcją maksymalnego szczytowego pochłaniania tlenu ($VO_{2max}$) po 15 miesiącach od przechorowania COVID-19 (roczny follow-up).

**Publikacja 4.**

W artykule przeglądowym zatytułowanym „***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19***” omówiono wpływ zakażenia SARS-CoV-2 na uszkodzenie mięśnia sercowego i występowanie powikłań zakrzepowo-zatorowych. Szczególną uwagę poświęcono zależnościom pomiędzy COVID-19 a niewydolnością serca (ang. heart failure - HF).

### 3.3. Podsumowanie

W przytoczonych artykułach podjęto próbę poszerzenia wiedzy na temat złożonych interakcji między COVID-19 i uszkodzeniem mięśnia sercowego, w szczególności patogenezy HF. Wyniki zaprezentowanych badań mogą przyczynić się do wczesnego wdrożenia odpowiednich procedur diagnostycznych, doboru spersonalizowanego leczenia oraz opracowania modelu opieki kardiologicznej i programów rehabilitacji nad osobami po zakażeniu SARS-CoV-2, a tym samym poprawy jakości ich życia.

## 4. STRESZCZENIE W JĘZYKU ANGIELSKIM/SUMMARY

### 4.1. Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was identified in December 2019 in Wuhan, China, and has evolved into a global health crisis. The World Health Organisation (WHO) declared the COVID-19 pandemic on March 11, 2020. It is estimated that the infection affected almost 800 million people around the world and caused approximately 7 million deaths. One of the most important problems after the pandemic is the long COVID syndrome. Long COVID is defined as the continuation or development of new symptoms at least 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting at least 2 months without any other explanation. Symptoms may reappear after initial recovery from COVID-19 or persist after illness; they may change or recur over time. Common symptoms include chronic fatigue, dyspnea, anosmia, ageusia, and cognitive dysfunction. Individuals recovering from COVID-19 also present exercise intolerance. Cardiopulmonary exercise testing (CPET) has become an important tool to evaluate the etiology of exercise intolerance. Furthermore, it is considered the gold standard for the assessment of physical fitness and evaluating the interaction of cardiovascular, respiratory, and metabolic systems. In view of the above, CPET may be a valuable tool to assess physical capacity in patients with long-COVID syndrome.

### 4.2. Objectives

The objective of the studies was to assess the impact of COVID-19 on the development of cardiovascular diseases and evaluate the factors influencing exercise intolerance after recovery.

**Article 1.**

The first study presented in the paper titled „***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction***” examines the mechanisms influencing exercise intolerance in patients recovering from COVID-19.

**Methods:** The study consists of 120 individuals recovering from COVID-19 at three to six months after diagnosis. The clinical examinations, laboratory tests, echocardiography, spiroergometry, and non-invasive body mass analysis were evaluated. Patients were divided into the two groups based on maximal predicted oxygen consumption ($\%VO_{2pred}$) in CPET: study group [n=47] presented with < $80\%VO_{2pred}$ and control group [n=73] presenting with ≥ $80\%VO_{2pred}$.

**Results:** The study showed that men have over twice the risk of persistent exercise intolerance than in women. Furthermore, decreased echocardiography parameters: late diastolic filling velocity (A wave), global longitudinal peak systolic strain (GLPS) and tricuspid annular plane systolic excursion (TAPSE) were related to limited exercise tolerance after COVID-19. The results of the multiple logistic regression model show that A wave and male gender were independently associated with $\%VO_{2pred}$.

**Conclusions:** Men have over twice the risk of persistent limited exercise tolerance in Long-COVID than women. The decreased (A) velocity, TAPSE, GLPS, and hydration status are related to limited exercise tolerance after COVID-19 in patients with normal left ventricular ejection fraction (LVEF).

**Article 2.**

In the study described in the paper "***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction***" the utility of CPET parameters in long COVID patients was analyzed.

**Methods:** The 146 patients (3 to 6 months after COVID-19 recovery) were divided into two groups: a group with long COVID symptoms [n=44] and a group without symptoms [n=102]. The clinical examinations, laboratory tests, echocardiography, spiroergometry, and non-invasive body mass analysis were evaluated.

**Results:** Patients with long COVID symptoms had significantly higher age, metabolic age, left atrial (LA) diameter, left ventricular mass index (LVMI), A wave, the ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion (E/E'), and a lower ratio of early to late diastolic transmitral flow velocity (E/A) compared to the control group. In CPET, long COVID patients presented lower forced vital capacity (FVC), maximal oxygen uptake ($VO_{2max}$), respiratory exchange ratio (RER), forced expiratory volume in one second (FEV1) and a higher Tiffeneau index

(FEV1/FVC%). The laboratory results pointed out that patients with long COVID symptoms also had a lower rate of red blood cells (RBC), a higher level of glucose, a lower glomerular filtration rate (GFR), and a higher level of high-sensitivity cardiac troponin T (hs-cTnT). On the multivariate model, only FEV1/FVC% independently predicted the long COVID symptoms. Using the receiver operating characteristic curve (ROC) analysis, the FEV1/FVC% $\geq$ 103 was the most powerful predictor of spiroergometry parameters (0.67 sensitive, 0.71 specific, AUC of 0.73; $p < 0.001$) in predicting the symptoms of long COVID.

**Conclusions:** Spiroergometry parameters are useful in diagnosing long COVID and differentiating it from cardiovascular disease.

**Article 3.**

The last study presented in the paper titled "***Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery***" is the continuation of previously mentioned study. Of the 146 patients included in the study described in publication 3., 82 completed one-year follow-up. The same diagnostic procedure was performed. Changes in laboratory parameters, echocardiography, spiroergometry and body composition analysis were analyzed after one year follow-up.

**Methods:** The aim of the study was to assess the mechanisms contributing to the limitation of exercise tolerance in patients who had COVID-19 after a one-year follow-up. Of 146 patients, 82 completed the follow-up.

**Results:** The study demonstrated that patients, after one-year follow-up, had significantly higher levels of hs-cTnT, LA diameter, RER, and total body water content percentage (TBW%) compared to the 3-month assessment. They also had lower FVC. Fat mass (FM), end-diastolic volume (EDV) and end-systolic volume (ESV) were independently associated with a decline in $VO_{2max}$ in one-year follow-up.

**Conclusions:** Higher left ventricular volumes and fat mass (%) were associated with a reduced maximal oxygen uptake ($VO_{2max}$) when assessed 15 months after COVID-19 recovery.

**Article 4.**

The review article titled "***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19***" discusses the impact of SARS-CoV-2 infection on myocardial damage and the occurrence of thromboembolic complications. Particular attention was paid to the relationship between COVID-19 and heart failure (HF).

### 4.3. Summary

The referenced papers attempt to broaden the understanding of complex interactions in COVID-19 and cardiac damage, particularly a development of HF. Thanks to the observed relationships, it will be possible to start appropriate diagnostic procedures early, select personalized treatment, develop a model of cardiac care and rehabilitation programs for people after SARS-CoV-2 virus infection, and thus improve the quality of their lives.

## 5. WPROWADZENIE

Pandemia koronawirusa (ang. Coronavirus Disease of 2019 - COVID-19) została uznana za zakończoną. Szacuje się, że infekcja dotknęła prawie 800 milionów osób na całym świecie oraz była przyczyną około 7 milionów zgonów [1]. Niestety, od kilku miesięcy na całym świecie obserwuje się ponowny wzrost zachorowań. W marcu 2025 odnotowano ponad 50 tysięcy potwierdzonych przypadków zakażeń na świecie, w tym około 2 tysiące w Polsce [2]. Analizując powyższe dane trzeba wziąć pod uwagę, że obecnie nie wykonuje się rutynowych testów na obecność koronawirusa (ang. severe acute respiratory syndrome coronavirus 2 - SARS-CoV-2). W związku z tym faktyczna liczba zakażeń może być jeszcze wyższa. Ponadto, naukowcy przewidują, że w najbliższych latach możemy stanąć w obliczu kolejnej pandemii [3]. Zmiany klimatyczne, zwiększona mobilność społeczeństwa, urbanizacja oraz globalizacja przyczyniają się do wzrostu ryzyka pojawienia się nowych, potencjalnie groźnych wirusów [4]. Wzrost temperatur, zmiany w ekosystemach i migracje dzikich zwierząt mogą sprzyjać rozprzestrzenianiu się patogenów na obszary dotychczas wolne od chorób zakaźnych [5-6].

Alarmująca sytuacja epidemiologiczna skłania naukowców do ciągłych badań nad wirusami, w tym SARS-CoV-2. COVID-19, mimo iż jest obecny na świecie od 2019 roku, wciąż kryje za sobą wiele tajemnic. Pierwsze przypadki zachorowań stwierdzono w grudniu 2019 w mieście Wuhan w Chinach. Choroba szybko rozprzestrzeniła się na inne obszary, a Światowa Organizacja Zdrowia 11 marca 2020 ogłosiła pandemię [7]. Uważa się, że wybuch pandemii pierwotnie rozpoczął się w wyniku transmisji odzwierzęcej. Następnie uznano, że transmisja między ludźmi odegrała główną rolę w wybuchu epidemii [8].

Zakażenie SARS-CoV-2 często przebiega bezobjawowo bądź skąpoobjawowo, ale może także prowadzić do ostrej niewydolności oddechowej, wstrząsu septycznego i zgonu [9]. Obecnie szacuje się, że nawet 33% zainfekowanych pacjentów nie ma symptomów zakażenia [10]. Najczęstszymi objawami są gorączka, kaszel, duszność, ból gardła, utrata węchu i/lub smaku, ból mięśniowo-szkieletowy, ból głowy i zmęczenie [11].

Wnikanie SARS-CoV-2 do komórek gospodarza jest możliwe poprzez interakcję białka S i enzymu konwertazy angiotensyny 2 (ang. angiotensin-converting enzyme 2 -

ACE2) [12]. ACE2, białko błonowe, jest obecne głównie w komórkach płuc, oskrzeli, naczyń krwionośnych, serca, nerek, jelit oraz jąder [13].

Obecność ACE2 w kardiomiocytach, komórkach śródbłonka, komórkach mięśni gładkich oraz adipocytach nasierdziowych może prowadzić do uszkodzenia mięśnia sercowego oraz jego dysfunkcji w wyniku zakażenia SARS-CoV-2 [rycina 1]. Negatywny wpływ wirusa na układ sercowo-naczyniowy został potwierdzony w wielu badaniach. Wykazano między innymi, że przebycie COVID-19 wiąże się ze zwiększonym ryzykiem zawału serca, udaru niedokrwiennego mózgu oraz zaburzeń rytmu serca [14,15]. Ponadto stwierdzono, że infekcja może pogorszyć stan kliniczny i rokowanie pacjentów z uprzednio rozpoznaną chorobą sercowo-naczyniową [16,17]. Szczególną grupę ryzyka stanowią chorzy z niewydolnością serca (ang. heart failure – HF). Infekcje wirusowe, w tym COVID-19 mogą powodować zaostrzenia HF [18]. Wykazano także, że nawet u 29% zakażonych pacjentów może występować ostre uszkodzenie nerek, co może również doprowadzić do zaostrzenia HF poprzez przeciążenie płynami [19]. Z drugiej strony, u niektórych pacjentów z COVID-19 obserwowano nowe przypadki HF [20,21]. Potencjalne czynniki mogące powodować objawy HF w tej grupie to niedokrwienie, zapalenie mięśnia sercowego, żylna choroba zakrzepowo-zatorowa oraz kardiomiopatia indukowana stresem [22,23]. Stan zapalny wywołany przez SARS-CoV-2 prowadzi do znacznej aktywacji płytek krwi poprzez burzę cytokinową. Mechanizm ten, wraz z uszkodzeniem śródbłonka powoduje rozwój koagulopatii, a także uszkodzenie serca, wywołując HF [24,25].

HF jest zespołem chorobowym charakteryzującym się występowaniem objawów podmiotowych i przedmiotowych spowodowanych nieprawidłowościami strukturalnymi lub czynnościowymi serca [26]. Jednym z objawów HF jest obniżenie wydolności fizycznej [27]. Pogorszoną tolerancję wysiłku zgłaszają również pacjenci z COVID-19 oraz osoby po przebyciu tej infekcji [28]. Istotnym problemem klinicznym staje się różnicowanie zespołu long COVID z HF de novo. Long COVID to zjawisko określone jako zespół objawów występujący u osób z potwierdzonym zakażeniem SARS-CoV-2 (zwykle 3 miesiące od zachorowania), który utrzymuje się przez co najmniej 2 miesiące i nie można go wyjaśnić w inny sposób. Oprócz zmniejszonej tolerancji wysiłku najczęściej występują przewlekłe zmęczenie, duszność, zaburzenia funkcji poznawczych, zaburzenia węchu i smaku, zaburzenia lękowe i depresyjne [29]. Badania sugerują, że objawy te mogą być wynikiem niepełnej regeneracji po uszkodzeniach wywołanych

przez wirusa, a także wpływem stylu życia, chorób współistniejących i stosowanych leków [30,31]. W zespole long COVID występują okresy remisji i zaostrzenia objawów, często związanych z nadmiernym wysiłkiem fizycznym.

Dotychczasowe analizy naukowców dowodzą, że long COVID to istotny problem społeczny. W jednym z badań wykazano, że long COVID wpływa na zdolność do podejmowania domowych obowiązków (84.3%), pracy (74.9%), samoopieki (50%), czy opieki nad dziećmi (35.8%) [32]. W związku z tym prowadzenie badań nad długoterminowymi skutkami pandemii COVID-19 ma kluczowe znaczenie dla funkcjonowania jednostek zarówno na poziomie pojedynczego gospodarstwa domowego, jak i dużych grup społecznych.

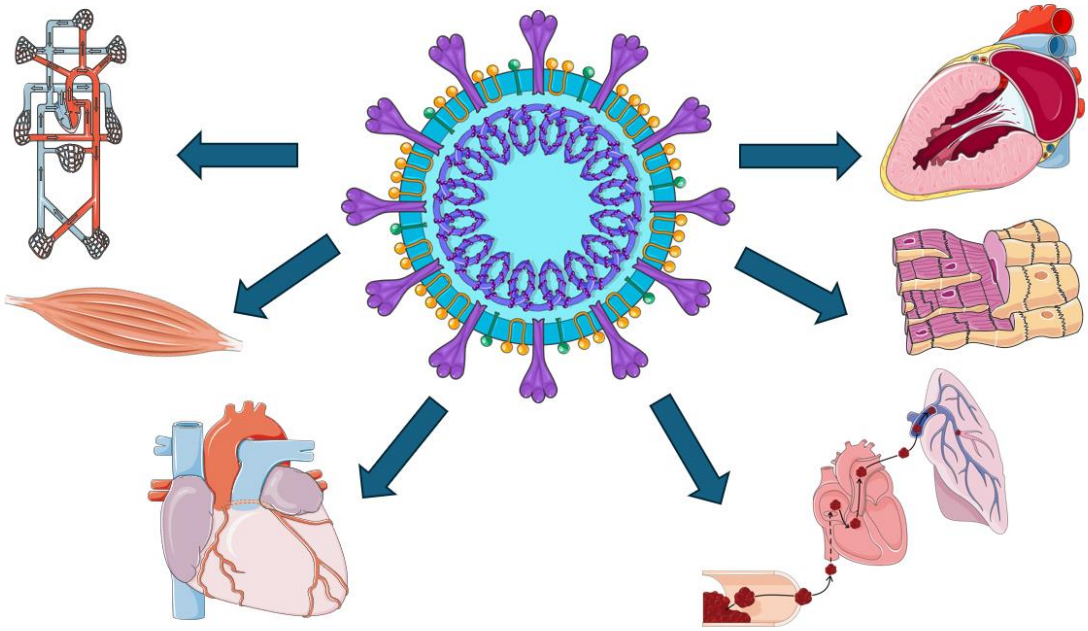
Jednym z zagadnień interesujących badaczy jest ocena wydolności fizycznej po COVID-19. Jak wspomniano wyżej, pogorszenie tolerancji wysiłku jest częstym objawem zespołu long COVID. Badaniem, które pozwala sprawdzić podłoże i mechanizmy zmniejszenia wydolności wysiłkowej jest test spiroergometryczny, znany także jako sercowo-płucny test wysiłkowy (ang. cardiopulmonary exercise testing – CPET). Oprócz elementów tradycyjnej próby wysiłkowej, możliwa jest ocena maksymalnego zużycia tlenu, produkcji dwutlenku węgla oraz wentylacji minutowej podczas wysiłku [33]. Ponadto, przed rozpoczęciem wysiłku na bieżni lub cykloergometrze przeprowadzana jest spirometria spoczynkowa. Badanie to jest uznawane za złoty standard w ocenie czynności układu oddechowego [34]. Biorąc pod uwagę powyższe, test spiroergometryczny dostarcza informacji na temat funkcjonowania układu oddechowego, krążenia oraz mięśni szkieletowych. Wyniki CPET są istotne dla opracowania programów rehabilitacji kardiologicznej, które mogą pomóc pacjentom w powrocie do pełnej sprawności [35]. Mają również znaczenie w kwalifikacji pacjentów do przeszczepu serca [36].

CPET może być również nieocenionym narzędziem w monitorowaniu pacjentów po przebytej infekcji COVID-19, dostarczając informacji dotyczących stanu klinicznego oraz w identyfikacji długoterminowych zaburzeń funkcjonalnych.

Celem rozprawy, na którą składają się 3 prace oryginalne i 1 praca poglądowa była ocena:

- czynników wpływających na pogorszenie tolerancji wysiłku u pacjentów po przebyciu COVID-19;
- użyteczności badania spiroergometrycznego w diagnostyce long COVID;

- parametrów pozwalających na zróżnicowanie zespołu long COVID z HFl;
- mechanizmów upośledzenia tolerancji wysiłku u ozdrowieńców COVID-19 po rocznej obserwacji.



Rycina 1. Powikłania i wpływ COVID-19 na funkcję mięśnia sercowego i wydolność wysiłkową. Rycina przygotowana przy użyciu Servier Medical Art objętego licencją Creative Commons 4.0.

# 6. CZĘŚĆ BADAWCZA

## 6.1. Założenia i cele pracy

W badaniu realizowano następujące cele badawcze:

1. Analiza mechanizmów wpływających na pogorszenie tolerancji wysiłku u pacjentów, którzy przebyli COVID-19;

2. Użyteczność badania spiroergometrycznego u pacjentów z zespołem long COVID;

3. Ocena mechanizmów wpływających na pogorszenie tolerancji wysiłku u pacjentów, którzy przebyli COVID-19 po rocznej obserwacji.

Cele szczegółowe badania:

- porównanie parametrów biochemicznych, echokardiograficznych, analizy składu masy ciała pomiędzy grupą, która osiągnęła ≥80% maksymalnego przewidywanego pochłaniania tlenu (%$VO_{2pred}$) w CPET, a grupą, która osiągnęła <80% $VO_{2pred}$;
- identyfikacja czynników wpływających na pogorszenie %$VO_{2pred;}$
- Ocena dynamiki zmian parametrów CPET oraz spirometrii spoczynkowej w zależności od obecności objawów long COVID;
- Porównanie parametrów biochemicznych, echokardiograficznych, analizy składu masy ciała pomiędzy grupą z objawami long COVID i grupą bezobjawową;
- Identyfikacja czynników, których obecność zwiększa prawdopodobieństwo wystąpienia long COVID;
- Ocena możliwości różnicowania objawów long COVID z objawami choroby układu sercowo-naczyniowego za pomocą CPET;
- porównanie parametrów biochemicznych, echokardiograficznych, spiroergometrycznych, analizy składu masy ciała przed i po rocznym follow-up;
- ocena przebiegu long COVID u badanej populacji;
- identyfikacja parametrów, które wpływały na obniżenie maksymalnego pochłaniania tlenu ($VO_{2max}$) po rocznej obserwacji (15 miesięcy po przechorowaniu COVID-19).

## 6.2. Materiał i metody

Wszystkie badania wymienione w niniejszym opracowaniu zostały przeprowadzone w Instytucie Centrum Zdrowia Matki Polki w Łodzi. Zgodę na przeprowadzenie badań

opisanych w publikacjach: „Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction", "Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction" oraz „Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery" wydała Komisja Bioetyczna przy Instytucie Centrum Zdrowia Matki Polki w Łodzi (numer zgody: PMMHRI-BCO.75/2020).

6.2.1. W publikacji pt. „***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction***" opisano przebieg badania, do którego włączono 120 pacjentów po spełnieniu zdefiniowanych kryteriów włączenia i braku kryteriów wyłączenia.

Kryteria włączenia:

- wiek pełnoletności (≥ 18 lat);
- potwierdzone przebyte zakażenie COVID-19 od 3 do 6 miesięcy przed włączeniem do badania;
- wyrażenie świadomej zgody na udział w badaniu.

Kryteria wyłączenia:

- niestabilne nadciśnienie tętnicze;
- niestabilna dławica piersiowa;
- ostry zator tętnicy płucnej;
- niewydolność serca;
- przebyty w ciągu 6 miesięcy zawał mięśnia sercowego;
- niestabilne zaburzenia rytmu serca;
- ostre zapalenie mięśnia sercowego lub osierdzia;
- czynne zapalenie wsierdzia;
- zaawansowany blok przedsionkowo-komorowy;
- zdiagnozowana kardiomiopatia (przerostowa, rozstrzeniowa, restrykcyjna, połogowa, tachyarytmiczna);
- udar mózgu, przemijający atak niedokrwienny (ang. transient ischemic attack – TIA), krwawienie śródmózgowe w wywiadzie;

- ciężka nadczynność lub niedoczynność tarczycy;
- ciąża lub laktacja;
- przewlekła choroba nerek w stadium IV, V wg NKF (ang. National Kidney Foundation) oraz pacjenci dializowani;
- udokumentowany proces nowotworowy;
- niezdolność pacjenta do współpracy i/lub udzielenia świadomej zgody na udział w badaniu;
- nadużywanie alkoholu lub leków;
- aktywna choroba autoimmunologiczna;
- przyjmowanie leków immunosupresyjnych, cytostatycznych, glikokortykosteroidów lub leków antyretrowirusowych;
- przeszczep szpiku lub przeszczep innego narządu w wywiadzie, leczenie preparatami krwiopochodnymi w ciągu ostatnich 6 miesięcy;
- aktywne ogólnoustrojowe zakażenie;
- nosicielstwo wirusa HBV (ang. hepatitis B virus), HCV (ang. hepatitis C virus) lub HIV (ang. human immunodeficiency virus) lub stwierdzenie pozytywnego wyniku na obecność antygenu HbS lub przeciwciał przeciwko wirusowi HCV;
- przebycie w ciągu ostatniego miesiąca zabiegu operacyjnego lub poważnego urazu;
- niepełnosprawność ruchowa uniemożliwiająca wykonanie badania spiroergometrycznego;
- pacjenci, którzy nie wyrazili świadomej zgody na udział w badaniu.

U pacjentów przeprowadzono badanie podmiotowe i przedmiotowe, wykonano badania laboratoryjne, badanie echokardiograficzne przezklatkowe, badanie spiroergometryczne oraz analizę składu ciała metodą bioimpedancji. Podzielono pacjentów na dwie grupy: pacjentów, którzy uzyskali $\geq 80\%VO_{2pred}$ [n=73] i pacjentów, którzy osiągnęli $<80\%$ $VO_{2pred}$ w badaniu spiroergometrycznym [n=47].

**Statystyka**

Zmienne o rozkładzie normalnym zostały przedstawione jako średnia arytmetyczna ± odchylenie standardowe, zmienne o rozkładzie skośnym zostały opisane jako mediana (górny i dolny kwartyl). Rozkład normalny weryfikowano testem Shapiro-Wilka. Do porównania dwóch grup zastosowano test t-Studenta dla zmiennych ciągłych o rozkładzie

normalnym oraz test U Manna-Whitney'a dla zmiennych o rozkładzie nienormalnym. Te dane kategoryczne zostały przetestowane za pomocą wstecznej krokowej wieloczynnikowej regresji logistycznej. W analizach za statystycznie istotne uznano wartości $p < 0.05$.

6.2.2. W kolejnej publikacji pt. „***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction***" przedstawiono badanie, do którego włączono 146 ochotników po spełnieniu obowiązujących kryteriów włączenia i niespełnienia kryteriów wyłączenia:

Kryteria włączenia:

- wiek pełnoletności (≥ 18 lat);
- potwierdzone przebyte zakażenie COVID-19 od 3 do 6 miesięcy przed włączeniem do badania;
- wyrażenie świadomej zgody na udział w badaniu.

Kryteria wyłączenia:

- niestabilne nadciśnienie tętnicze;
- niestabilna dławica piersiowa;
- ostry zator tętnicy płucnej;
- niewydolność serca;
- przebyty w ciągu 6 miesięcy zawał mięśnia sercowego;
- niestabilne zaburzenia rytmu serca;
- ostre zapalenie mięśnia sercowego lub osierdzia;
- czynne zapalenie wsierdzia;
- zaawansowany blok przedsionkowo-komorowy;
- zdiagnozowana kardiomiopatia (przerostowa, rozstrzeniowa, restrykcyjna, połogowa, tachyarytmiczna);
- udar mózgu, TIA, krwawienie śródmózgowe w wywiadzie;
- ciężka nadczynność lub niedoczynność tarczycy;
- ciąża lub laktacja;
- przewlekła choroba nerek w stadium IV, V wg NKF oraz pacjenci dializowani;
- udokumentowany proces nowotworowy;

- niezdolność pacjenta do współpracy i/lub udzielenia świadomej zgody na udział w badaniu;
- nadużywanie alkoholu lub leków;
- aktywna choroba autoimmunologiczna;
- przyjmowanie leków immunosupresyjnych, cytostatycznych, glikokortykosteroidów lub leków antyretrowirusowych;
- przeszczep szpiku lub przeszczep innego narządu w wywiadzie, leczenie preparatami krwiopochodnymi w ciągu ostatnich 6 miesięcy;
- aktywne ogólnoustrojowe zakażenie;
- nosicielstwo wirusa HBV, HCV lub HIV bądź stwierdzenie pozytywnego wyniku na obecność antygenu HbS lub przeciwciał przeciwko wirusowi HCV;
- przebycie w ciągu ostatniego miesiąca zabiegu operacyjnego lub poważnego urazu;
- niepełnosprawność ruchowa uniemożliwiająca wykonanie badania spiroergometrycznego;
- pacjenci, którzy nie wyrazili świadomej zgody na udział w badaniu.

U pacjentów wykonano badanie podmiotowe i przedmiotowe, badania laboratoryjne, badanie echokardiograficzne przezklatkowe i CPET. Ponadto przeprowadzono analizę składu masy ciała metodą bioimpedancji. Uczestników badania podzielono na dwie grupy: pacjentów z objawami long COVID (przynajmniej jeden z objawów: duszność, zmęczenie, ból w klatce piersiowej, ból mięśni, zaburzenia poznawcze, zaburzenia węchu i smaku) [n=44] oraz pacjentów bezobjawowych [n=102].

**Statystyka**

Zgodność z rozkładem normalnym wszystkich zmiennych została obliczona za pomocą testu Shapiro-Wilka. Do porównania dwóch grup zastosowano test t-Studenta dla zmiennych ciągłych o rozkładzie normalnym oraz test U Manna-Whitney'a dla zmiennych o rozkładzie nienormalnym. Czynniki, które powodowały objawy long COVID, były identyfikowane przy użyciu analizy jednoczynnikowej oraz wieloczynnikowej (model regresji logistycznej). Przeprowadzono analizy krzywej charakterystyki operacyjnej odbiornika (ang. ROC – receiver operating characteristic curve) w celu określenia czułości i swoistości. Aby zredukować błąd związany z wiekiem między grupą long COVID a populacją bez long COVID, zastosowano algorytm

najbliższego sąsiada. Parametry, które spełniały następujące kryteria: (1) były statystycznie istotne w analizie jednoczynnikowej oraz (2) pole pod krzywą ROC (ang. area under the curve - AUC) wynosiło co najmniej 0.630, kwalifikowano do modelu wieloczynnikowego. Dla tych parametrów określono punkty odcięcia na podstawie indeksu Youdena krzywej ROC. Wyniki dla wybranych parametrów przekształcono w zmienne dychotomiczne na podstawie punktu Youdena. Test chi-kwadrat został użyty do porównania zmiennych dychotomicznych między grupami. W analizach za statystycznie istotne uznano wartości $p < 0.05$.

6.2.3. W badaniu opisanym w publikacji pt. „***Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery***" oceniono po roku pacjentów, którzy brali udział w badaniu opisanym w publikacji numer 2. Follow-up ukończyło 82 uczestników (56% włączonych uprzednio pacjentów). Przeprowadzono takie samo postępowanie diagnostyczne jak podczas pierwszego badania.

**Statystyka**

Test Shapiro-Wilka ocenił normalność rozkładu. Do porównania dwóch grup zastosowano test t-Studenta dla zmiennych ciągłych o rozkładzie normalnym oraz test U Manna-Whitney'a dla zmiennych o rozkładzie nienormalnym. Te dane kategoryczne zostały przetestowane za pomocą wstecznej krokowej wieloczynnikowej regresji logistycznej. W analizach za statystycznie istotne uznano wartości $p < 0.05$.

## 6.3. Ocena aparaturowa

### 6.3.1. Analiza laboratoryjna

Próbki krwi pobrano do probówek z politereftalanu etylenu zawierających kwas etylenodiaminotetraoctowy (ang. ethylenediaminetetraacetic acid – EDTA). Zebrane próbki krwi dokładnie wymieszano, przechowywano w temperaturze 4°C i odwirowano w ciągu 6 godzin. Uzyskane próbki osocza natychmiast zamrożono i przechowywano w temperaturze -80°C aż do momentu przeprowadzenia pomiarów. Badania laboratoryjne wykonano w laboratorium szpitalnym po upływie co najmniej 12 godzin od ostatniego

posiłku. Stężenia biomarkerów mierzono za pomocą dedykowanych testów immunoenzymatycznych (ang. enzyme-linked immunosorbent assay – ELISA).

### 6.3.2. Echokardiografia przezklatkowa

Badanie echokardiograficzne przezklatkowe wykonano za pomocą systemu Vivid E95 (GE Healthcare, Chicago, IL, USA). Pomiary wykonano zgodnie z wytycznymi American Society of Echocardiography (ASE) i European Association of Echocardiography (EAE) [37]. Dokonano pomiarów lewej komory (ang. left ventricular internal diameter – LVID), przegrody międzykomorowej (ang. interventricular septum - IVS) i tylnej ściany lewej komory (ang. left ventricular posterior wall - LVPW). Objętość lewej komory oraz frakcję wyrzutową (ang. left ventricular ejection fraction - LVEF) obliczono z pomocą dwuwymiarowej dwupłaszczyznowej zmodyfikowanej metody Simpsona na podstawie projekcji cztero- i dwujamowej. Objętość lewego przedsionka (ang. left atrial volume - LAV) określono na podstawie projekcji dwujamowej i czterojamowej w fazie końcowoskurczowej, stosując zmodyfikowaną metodę Simpsona. Każdą wartość LAV indeksowano przez powierzchnię ciała (ang. left atrial volume index - LAVi). Indeks masy lewej komory (ang. left ventricular mass index - LVMI) obliczono, dzieląc masę lewej komory (w gramach) przez powierzchnię ciała. Dodatkowe analizowane parametry echokardiograficzne obejmowały: maksymalną prędkość wczesnego napływu mitralnego (ang. early diastolic filling velocity - E) i maksymalną prędkość fali przedsionkowej (ang. late diastolic filling velocity - A); stosunek maksymalnej prędkości wczesnego napływu mitralnego do wczesnej prędkości pierścienia mitralnego (ang. ratio of early diastolic filling velocity to early diastolic mitral annular velocity - E/E'); stosunek wczesnego do późnego przepływu transmitralnego (E/A); oraz czas deceleracji (Dec) i czas akceleracji (Ats). Globalne podłużne szczytowe odkształcenie lewej komory (ang. global longitudinal peak systolic strain - GLPS) uzyskano za pomocą echokardiografii śledzenia plamki (speckle-tracking). Oceniono także średnice aorty wstępującej (ang. ascending aorta - AA), opuszki aorty (ang. aortic bulb - AB), pnia płucnego (ang. main pulmonary artery - MPA) i żyły głównej dolnej (ang. inferior vena cava - IVC). Funkcję prawej komory (ang. right ventricle - RV) oceniono poprzez pomiar amplitudy skurczowego przemieszczenia pierścienia zastawki trójdzielnej (ang. tricuspid annular plane systolic excursion - TAPSE) oraz echokardiografii Dopplera tkankowego (ang. tissue Doppler echocardiography - TDE). Dodatkowo obliczono pole powierzchni prawego przedsionka (ang. right atrial area -

RAA) i średnicę drogi odpływu prawej komory (ang. right ventricular outflow tract - RVOT).

### 6.3.3. Badanie spiroergometryczne (CPET)

CPET przeprowadzono przy użyciu ergometru rowerowego Bike M (CORTEX Biophysik GmbH, Lipsk, Niemcy). Analizy gazów oddechowych dokonano za pomocą systemu METALYZER 3B (CORTEX Biophysik GmbH, Lipsk, Niemcy) wspomaganego oprogramowaniem MetaSoft Studio (wersja 5.8.3) opracowanym przez CORTEX systems. Przed każdym testem system był kalibrowany za pomocą standardowej mieszaniny gazów o znanych stężeniach. Analizator gazów wydechowych był wewnętrznie kalibrowany bezpośrednio przed każdym pomiarem. Zarówno objętość gazów, jak i sensor przepływu były kalibrowane tuż przed testem, a ich kalibrację weryfikowano dwa razy w roku. Po 5 minutach odpoczynku na ergometrze rozpoczęto ćwiczenia przy obciążeniu 50 W, które zwiększano o 25 W co 3 minuty. Przed testem wysiłkowym na ergometrze rowerowym wykonano spirometrię spoczynkową. Oceniono natężoną objętość wydechową pierwszosekundową (ang. forced expiratory volume in one second - FEV1) oraz natężoną pojemność życiową (ang. forced vital capacity - FVC). Zarejestrowano także wskaźnik FEV1/FVC, znany jako wskaźnik Tiffeneau. W trakcie CPET monitorowano ciśnienie krwi za pomocą sfigmomanometru Exacta (Rudolf Riester GmbH, Jungingen, Niemcy), a także częstotliwość rytmu serca (ang. heart rate - HR) i 12-odprowadzeniowy elektrokardiogram przy użyciu ergospirometru Meta control 3000 (CORTEX Biophysik GmbH, Lipsk, Niemcy). Jednym z kluczowych pomiarów uzyskanych podczas CPET jest maksymalne szczytowe pochłanianie tlenu (ang. maximal oxygen uptake - $VO_{2max}$), które reprezentuje najwyższy poziom metabolizmu tlenowego możliwy do osiągnięcia przy zaangażowaniu dużych grup mięśniowych. Jeśli na krzywej poboru tlenu nie jest widoczna wyraźna plateau, jako substytut $VO_{2max}$ można wykorzystać najwyższy osiągnięty $VO_2$, zwany $VO_{2peak}$. Ponadto oceniono kilka innych istotnych parametrów CPET: wymianę wentylacyjną (ang. ang. ventilatory exchange - VE), eliminację dwutlenku węgla (ang. carbon dioxide production - $VCO_2$), współczynnik wymiany oddechowej (ang. respiratory exchange ratio - RER), próg beztlenowy (ang. anaerobic threshold - AT), pobór tlenu na progu beztlenowym (ang. oxygen uptake at anaerobic threshold - $VO_2AT$) oraz nachylenie wentylacji minutowej do produkcji dwutlenku węgla ($VE/VCO_2$ slope).

### 6.3.4. Analiza składu ciała

Do nieinwazyjnej analizy składu masy ciała użyto analizatora składu ciała (Tanita Pro, Tokio, Japonia). Urządzenie to dostarcza szacunkowych wartości dla każdego mierzonego parametru, wykorzystując metodę absorpcjometrii rentgenowskiej o podwójnej energii (ang. dual energy X-ray absorptiometry - DXA), szacunkową wartość dla całkowitej zawartości wody w organizmie, mierzoną metodą rozcieńczenia oraz szacunkową wartość dla tłuszczu trzewnego, wykorzystując metodę bioimpedancji elektrycznej (ang. bioelectrical impedance analysis - BIA). Badanych proszono o stanie boso w stabilnej pozycji. Urządzenie dostarczało odczyty masy ciała dla różnych segmentów ciała — kończyn i korpusu — stosując algorytm uwzględniający impedancję, wiek i wzrost, w celu oszacowania zawartości tkanki tłuszczowej (ang. fat mass - FM) oraz beztłuszczowej masy ciała (ang. fat free mass - FFM). Uzyskano również następujące parametry: zawartość wody zewnątrzkomórkowej (ang. extracellular water - ECW), wody wewnątrzkomórkowej (ang. intracellular water - ICW) oraz całkowitej wody w organizmie (ang. total body water - TBW). ECW odnosi się do płynów ciała znajdujących się poza komórkami. Kompartment ICW obejmuje wszystkie płyny zamknięte w komórkach przez ich błony plazmatyczne. TBW to całkowita ilość płynów w ciele osoby, wyrażona jako procent jej całkowitej masy. Dodatkowo obliczono stosunek ECW/TBW%.

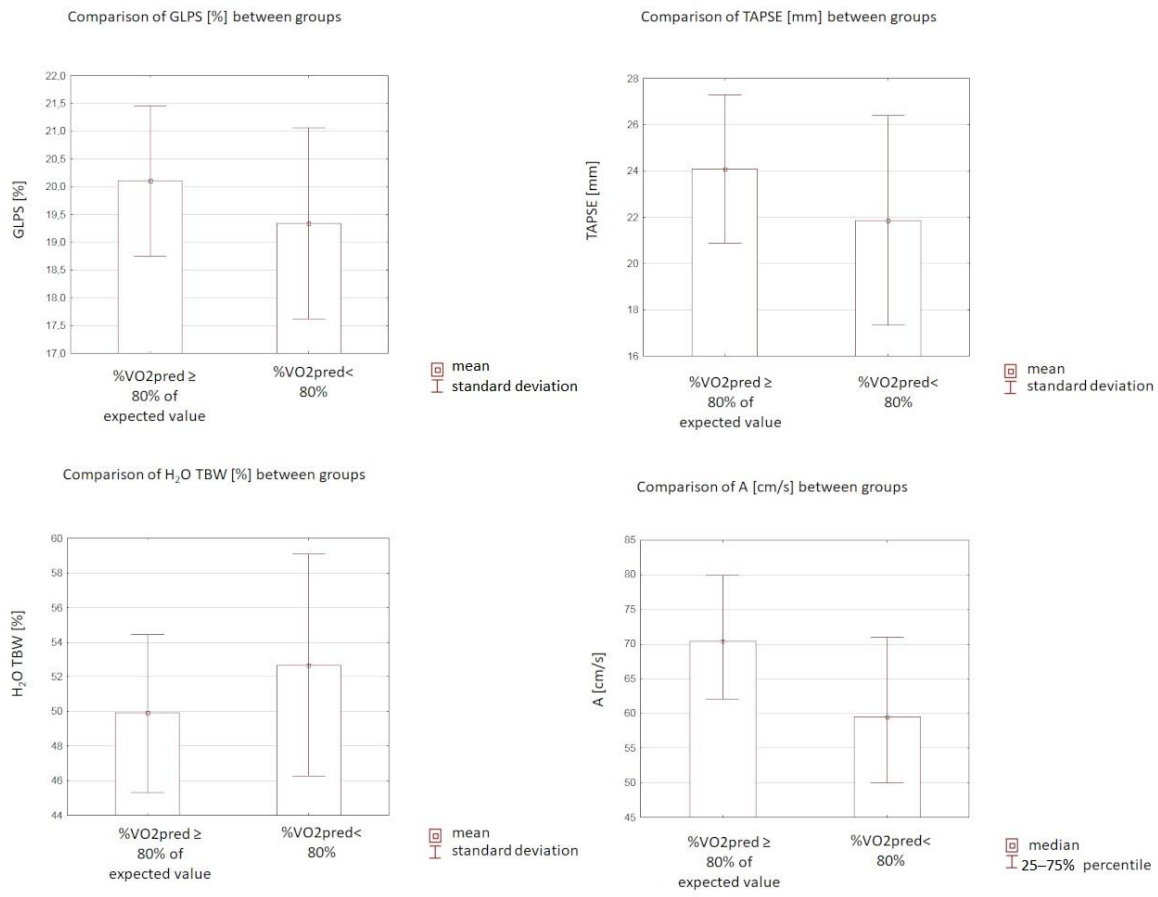
## 6.4. Wyniki

Niniejsza praca doktorska opiera się na danych zebranych w trakcie pracy w Klinice Kardiologii i Wad Wrodzonych Dorosłych Instytutu Centrum Zdrowia Matki Polki w Łodzi w latach 2020-2023. Szczegółowy opis metodyki oraz analiza, interpretacja i dyskusja dotycząca wyników przeprowadzonych badań, wraz z dokumentacją w formie tabel i rycin, znajduje się w trzech pracach oryginalnych stanowiących podstawę niniejszej rozprawy doktorskiej. Prace oryginalne zostały uzupełnione zgodną tematycznie publikacją poglądową.

### 6.4.1. Publikacja 1 – stanowi realizację celu badawczego numer 1

Gryglewska-Wawrzak K, Sakowicz A, Banach M, Maciejewski M, Bielecka-Dabrowa A. *Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction. Biomedicines.* 2022 Dec 15;10(12):3257.

W ramach badania opisanego w publikacji „Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction" analizowano obecność czynników, które powodują upośledzenie tolerancji wysiłku w badaniu spiroergometrycznym u chorych po COVID-19, u których nie stwierdzono dotychczas niewydolności serca. Badanie objęło 120 ochotników, którzy przebyli COVID-19 od 3 do 6 miesięcy przed hospitalizacją. Podzielono ich na dwie grupy: pacjentów, którzy osiągnęli <80% $VO_{2pred}$ w badaniu spiroergometrycznym [n=47, mediana wieku 49 lat (ang. interquartile range - IQR 30-65), 53% mężczyzn] i grupę kontrolną, która uzyskała ≥ 80%$VO_{2pred}$ [n=73, mediana wieku 55 lat (IQR 47-64), 29% mężczyzn]. Wykazano, że liczba mężczyzn i procentowa zawartość TBW w organizmie są istotnie wyższe w grupie badanej w porównaniu do grupy kontrolnej [53 versus 29%, p = 0.007 i 52.67 (±6.41) vs. 49.89 (±4.59) %, p = 0.02; odpowiednio]. Z przedstawionych analiz wynika również, że pacjenci z %$VO_{2pred}$ < 80% mieli obniżone wartości GLPS, TAPSE i fali A [19.34 (±1.72) % vs. 20.10 (±1.35) %, p = 0.03; 21.86 (±4.53) vs. 24.08 (±3.20) mm, p = 0.002 i mediana 59.5 (IQR: 50.0–71.0) vs. 70.5 (IQR: 62.0–80.0) cm/s, p = 0.004; odpowiednio] w porównaniu do grupy, która osiągnęła %$VO_{2pred}$ ≥ 80% [rycina 2].




Rycina 2. Porównanie wybranych parametrów echokardiograficznych i analizy masy ciała pomiędzy badanymi grupami. $\%VO_{2pred}$ — procent przewidywanego maksymalnego zużycia tlenu; GLPS— globalne podłużne szczytowe odkształcenie skurczowe lewej komory; TAPSE — amplituda skurczowego przemieszczenia pierścienia zastawki trójdzielnej; A – maksymalna prędkość fali przedsionkowej; H2O TBW – zawartość całkowitej wody w organizmie.

Na podstawie analizy wieloczynnikowej wykazano, że fala A (OR 0.40, 95%CI: 0.17–0.95; p = 0.03) i płeć męska (OR 2.52, 95%CI: 1.07–5.91; p = 0.03) są niezależnie związane z $\%VO_{2pred}$ [tabela 1].

| **Analiza wieloczynnikowa** | | | | |
|---|---|---|---|---|
| **Zmienna** | **Exp(B)–OR** | **95% CI** | | **P** |
| A [cm/s] | 0.40 | 0.17 | 0.95 | 0.03 |
| płeć męska [%] | 2.52 | 1.07 | 5.91 | 0.03 |

Tabela 1. Analiza wieloczynnikowa zmiennych wpływających na $\%VO_{2pred.}$ A – maksymalna prędkość fali przedsionkowej; $\%VO_{2pred}$ — procent przewidywanego maksymalnego zużycia tlenu.

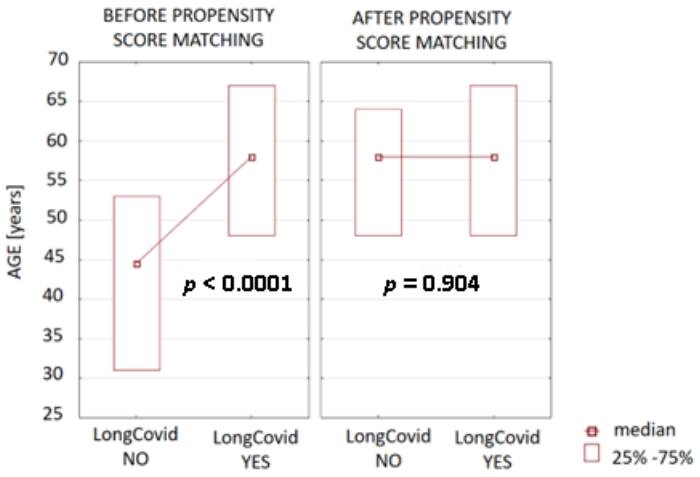
### 6.4.2. Publikacja 2 – stanowi realizację celu badawczego numer 2

Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bytyçi I, Bielecka-Dabrowa A. *Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction. J Clin Med.* 2023 Jun 20;12(12):4160.

W badaniu opisanym w pracy „Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction" analizowano użyteczność CPET u chorych z zespołem long COVID. Do badania włączono 146 ochotników od 3 do 6 miesięcy po przechorowaniu COVID-19. Podzielono ich na grupę z objawami long COVID [n=44, mediana wieku 58 lat (IQR 48-67), 41% mężczyzn] oraz grupę bezobjawową [n=102, mediana wieku 44 lata (IQR 31-53), 36% mężczyzn]. Wykazano, iż pacjenci z objawami long COVID byli starsi niż grupa bezobjawowa [58 vs. 44 lata; $p < 0.0001$], mieli wyższe wartości wieku metabolicznego [53 vs. 45 lat; $p = 0.02$], LA [37 vs. 35 mm; $p = 0.04$], LVMI [83 vs. 74 g/m$^2$, $p = 0.04$], fali A [69 vs. 64 cm/s, $p = 0.01$], E/E' [7.35 vs. 6.05; $p = 0.01$] i niższą wartość E/A [1.05 vs. 1.31; $p = 0.01$].

W badaniu CPET pacjenci z long COVID prezentowali obniżony poziom FVC [3.6 vs. 4.3 L; $p < 0.0001$], $VO_{2max}$ [21 vs. 23 mL/min/kg; $p = 0.04$], RER [1.0 vs. 1.1; $p = 0.04$], FEV1 [2.90 vs. 3.25 L; $p = 0.04$] oraz wyższy poziom wskaźnika Tiffeneau (FEV1/FVC%) [106 vs. 100%; $p = 0.0002$]. Badania laboratoryjne wykazały zmniejszoną liczbę erytrocytów [4.4 vs. 4.6 × 10$^6$/uL; $p = 0.01$]; zwiększony poziom glikemii na czczo [92 vs. 90 mg/dL; $p = 0.03$] i hs-cTnT [6.1 vs. 3.9 pg/mL; $p = 0.04$] oraz obniżony GFR [88 vs. 95; $p = 0.03$] u pacjentów z long COVID.

Aby zredukować różnicę wiekową między grupą z objawami long COVID a grupą bezobjawową zastosowano jednoczesne dopasowanie na zasadzie najbliższego sąsiada według wyniku skłonności (propensity score matching). Estymację wyniku skłonności przeprowadzono za pomocą regresji logistycznej. Następnie pacjentów dopasowano pod względem wieku, aby zweryfikować, czy obserwowane różnice między grupami przed dopasowaniem dla następujących zależnych od wieku parametrów, tj. A, $HR_{max}$, $VO_{2max}$, FEV1, FVC, FEV1/FVC [%], a także RER i GFR, będą podobne po korekcji wiekowej. Różnice w wieku między grupą long COVID a grupą bez objawów przed i po dopasowaniu przedstawiono na rycinie 3.




Rycina 3. Różnice w wieku między grupami przed i po dopasowaniu.

Analiza wykazała, że badane grupy, dopasowane pod względem wieku, nie różniły się pod względem następujących parametrów: $HR_{max}$, $VO_{2max}$ i RER. Pozostałe analizowane parametry różniły się istotnie między grupami. Wyniki przedstawiono w tabeli 2.

| **Zmienna** | **Pacjenci z objawami long COVID [n=44]** | **Pacjenci bez objawów long COVID [n=102]** | **P** |
|---|---|---|---|
| A [cm/s] | (60.00–83.00), 69.00 * | (58–78), 67 * | 0.04 |
| FVC [L] | (3.08–4.27), 3.53 * | 3.80–4.30), 4.26 * | 0.0001 |
| FEV1 [L] | (2.55–3.54), 2.90 * | (2.91–3.53), 3.11 * | 0.045 |
| FEV1/FVC [%] | (99.00–112.00), 106.50 * | (95.00–102.00), 96.00 * | <0.0001 |
| GFR [mL/min/1.73m$^2$] | (76.10–98.80), 88.25 * | (79.88–109.80), 93.20 * | 0.04 |

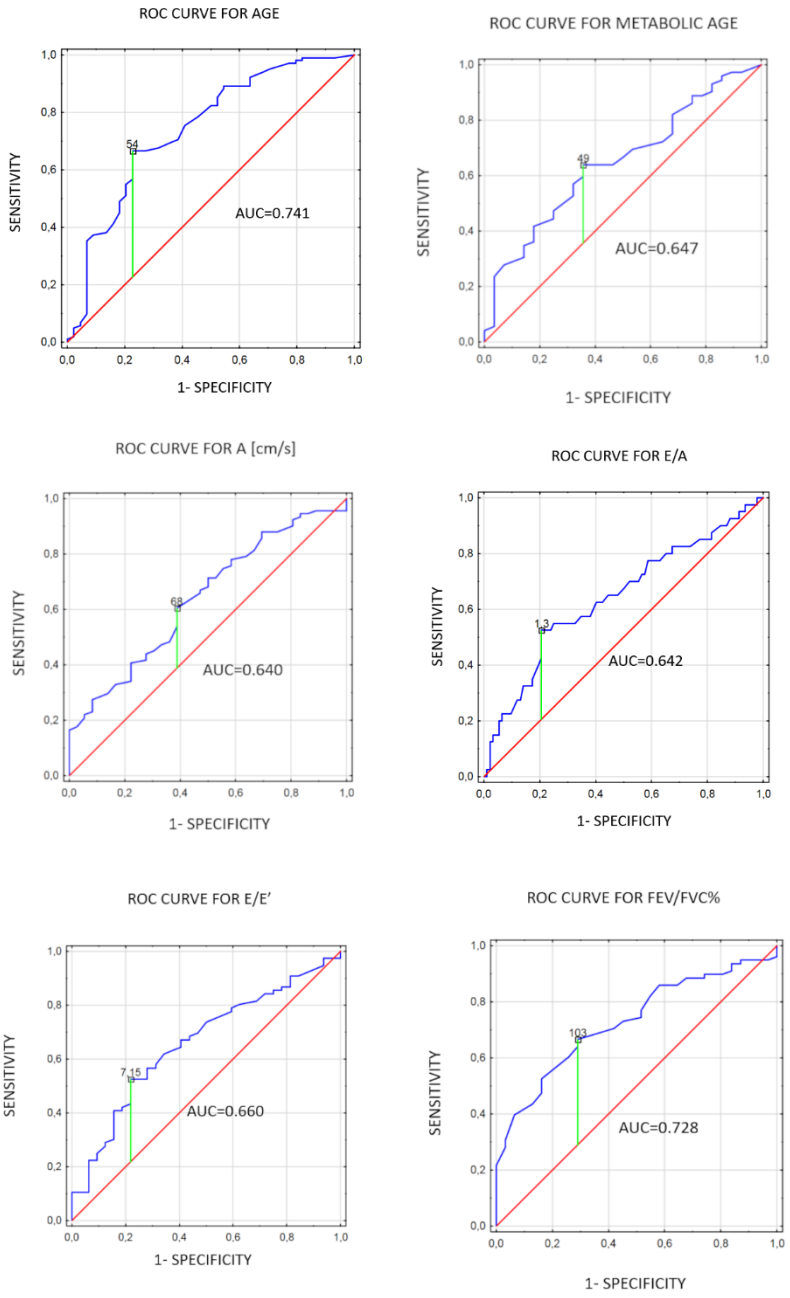
Tabela 2. Istotne różnice między badanymi grupami po dopasowaniu na podstawie wyniku skłonności. *—mediana; wartości o rozkładzie nie-normalnym są wyrażone jako mediana (zakres). Wartości o rozkładzie normalnym są wyrażone jako średnia ± odchylenie standardowe (SD). A—maksymalna prędkość fali przedsionkowej; FVC—natężona pojemność życiowa; FEV1—natężona objętość wydechowa pierwszosekundowa; FEV1/FVC—stosunek natężonej objętości wydechowej pierwszosekundowej do natężonej pojemności życiowej; GFR—wskaźnik przesączania kłębuszkowego.

Parametry spełniające następujące kryteria: (1) były statystycznie istotne w analizie jednoczynnikowej oraz (2) pole pod krzywą ROC (ang. area under the curve - AUC) wynosiło co najmniej 0,630, zostały zakwalifikowane do modelu wieloczynnikowego.

Tylko 6 parametrów spełniło oba kryteria, tj. wiek, wiek metaboliczny, A, E/A, E/E' oraz FEV1/FVC%. Dla tych parametrów określono punkty odcięcia na podstawie indeksu Youdena krzywej ROC, tj. wiek < 54 lat, wiek metaboliczny < 49 lat, A < 68 cm/s, E/A < 1,3, E/E' < 7,15 oraz FEV1/FVC% > 103. Ze względu na zaobserwowane korelacje między A [cm/s] a E/A oraz między A [cm/s] a E/E' (R Spearman = -0,54; p < 0,0001 oraz R Spearman = 0,34; p = 0,002), w analizie wieloczynnikowej uwzględniono jedynie wiek < 54 lat, wiek metaboliczny < 49 lat, A < 68 cm/s oraz FEV1/FVC% > 103. W analizie wieloczynnikowej wykazano, że tylko FEV1/FVC% (OR 6.27, 95% CI: 2.64–14.86; p < 0.001) jest niezależnym czynnikiem wpływającym na pojawienie się objawów zespołu long COVID [tabela 3]. Przy użyciu krzywej ROC udowodniono, że wartość FEV1/FVC% ≥ 103 jest najbardziej przydatnym parametrem CPET (0.67 czułości, 0.71 swoistości, AUC 0.73; p < 0.001) w przewidywaniu objawów long COVID [rycina 4].

| **Analiza wieloczynnikowa** | | | | |
|---|---|---|---|---|
| **Zmienna** | **Exp(B)–OR** | **95% CI** | | **P** |
| FEV1/FVC [%] | 6.27 | 2.64 | 14.86 | <0.001 |

Tabela 3. Analiza wieloczynnikowa zmiennych wpływających na pojawienie się objawów zespołu long COVID. FEV1/FVC—stosunek natężonej objętości wydechowej pierwszosekundowej do natężonej pojemności życiowej.




Rycina 4. Krzywe charakterystyki operacyjnej odbiornika (ROC) dla parametrów spiroergometrycznych u pacjentów z objawami long COVID. A— maksymalna prędkość fali przedsionkowej; E/A—stosunek prędkości wczesnego do późnego rozkurczowego przepływu mitralnego; E/E'—stosunek maksymalnej prędkości wczesnego rozkurczowego przepływu mitralnego do maksymalnej prędkości wczesnego rozkurczowego ruchu pierścienia mitralnego; FEV1/FVC—stosunek natężonej objętości wydechowej pierwszosekundowej do natężonej pojemności życiowej.

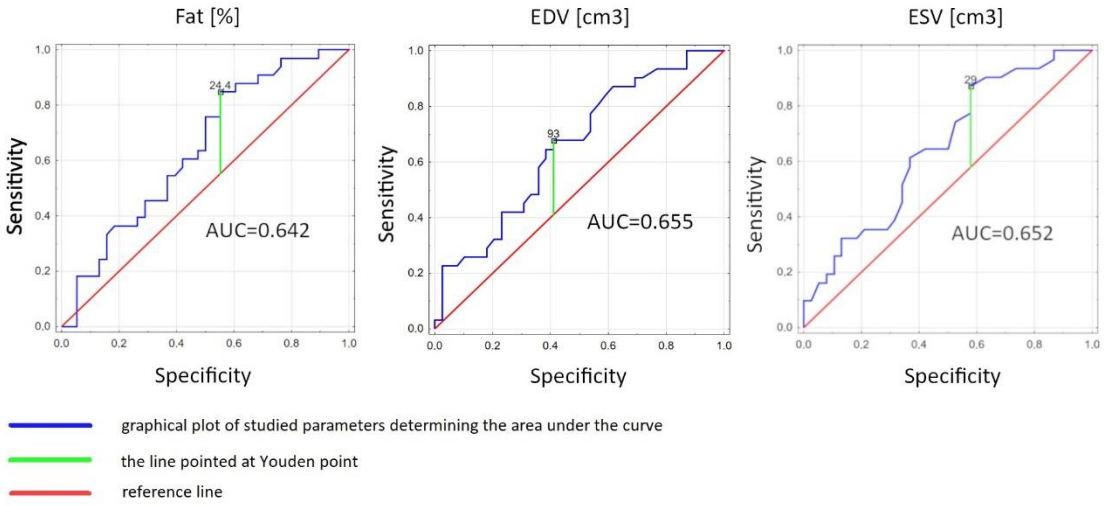
### 6.4.3. Publikacja 3 – stanowi realizację celu badawczego numer 3

Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bielecka-Dabrowa A. *Predictors of Long-COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery. J Clin Med.* 2023 Dec 14;12(24):7689.

Praca pt. „Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery" stanowi kontynuację badania opisanego w ramach publikacji „Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction". Badanie miało na celu ocenę tolerancji wysiłku u tej samej grupy ochotników po rocznej obserwacji. Spośród 146 pacjentów (38% mężczyzn, 62% kobiet), którzy byli hospitalizowani od 3 do 6 miesięcy po przebyciu COVID-19, 82 osoby (56%) (35 mężczyzn, 47 kobiet) oceniono po rocznej obserwacji. Wykazano, że pacjenci po rocznym follow-up prezentowali wyższe wartości hs-cTnT ($p = 0.03$), LA ($p = 0.03$), RER ($p = 0.008$) oraz TBW% ($p < 0.0001$) w porównaniu do poprzedniej analizy. Ponadto mieli mniejszą wartość FVC ($p = 0.02$). Parametry, które były statystycznie istotne w analizie jednoczynnikowej zostały zakwalifikowane do modelu wieloczynnikowego. Wykazano, że FM% (OR 2.16, 95% CI: 0.51–0.77; $p = 0.03$), EDV (OR 2.38, 95% CI 0.53–0.78; $p = 0.02$) i ESV (OR 2.3, 95% CI: 0.52–0.78; $p = 0.02$) były niezależnie powiązane ze spadkiem maksymalnego pochłaniania tlenu po rocznym follow-up. Wyniki analizy wieloczynnikowej przedstawiono w tabeli 4 i na rycinie 5.

| **Analiza wieloczynnikowa** | | | | |
|---|---|---|---|---|
| **Zmienna** | **Exp(B)–OR** | **95% CI** | | **P** |
| FM [%] | 2.16 | 0.51 | 0.77 | 0.03 |
| EDV [ml] | 2.38 | 0.53 | 0.78 | 0.02 |
| ESV [ml] | 2.30 | 0.52 | 0.78 | 0.02 |

Tabela 4. Analiza wieloczynnikowa zmiennych wpływających na spadek maksymalnego pochłaniania tlenu ($VO_{2max.}$). EDV – objętość późno-rozkurczowa lewej komory; ESV – objętość późno-skurczowa lewej komory; FM – zawartość tkanki tłuszczowej.




Rycina 5. Krzywa charakterystyki operacyjnej odbiornika (ROC) dla zmiennych: zawartość tkanki tłuszczowej (%), objętość końcoworozkurczowa (EDV) oraz objętość końcowoskurczowa (ESV), ukazująca ich potencjał diagnostyczny. AUC—pole pod krzywą ROC.

### 6.5. Podsumowanie i dyskusja

Przedstawione badanie jest jednym z pierwszych, na podstawie którego wykazano związek między przebyciem COVID-19 a obniżeniem poziomu wydolności fizycznej. Zidentyfikowano czynniki, które wpływają na pogorszenie tolerancji wysiłku po przechorowaniu COVID-19 oraz pojawienie się objawów zespołu long COVID. Ponadto udowodniono użyteczność badania spiroergometrycznego w różnicowaniu zespołu long COVID z HF.

To także pierwsza analiza uwzględniająca tak szeroki panel badań diagnostycznych (echokardiografia, spiroergometria, analiza składu ciała metodą bioimpedancji) u pacjentów po przechorowaniu COVID-19.

Głównym założeniem badań wchodzących w skład niniejszej rozprawy było przeprowadzenie testów spiroergometrycznych u pacjentów, którzy przebyli COVID-19. CPET jest najbardziej wiarygodnym badaniem pozwalającym na ustalenie przyczyn zmniejszonej tolerancji wysiłku/duszności niejasnego pochodzenia [38]. Pogorszenie tolerancji wysiłku jest jednym z najczęściej zgłaszanych objawów zespołu pokowidowego. W dostępnej literaturze opisano około 200 objawów, które mogą towarzyszyć zespołowi long COVID. Oprócz upośledzenia tolerancji wysiłku, jednymi z najczęstszych symptomów są zaburzenia koncentracji („mgła mózgowa”), bóle mięśniowo-stawowe, zawroty głowy, kołatania serca, zaburzenia snu, zaburzenia węchu

i smaku, a także zaburzenia depresyjno-lękowe [39,40]. Pomimo licznych analiz dotyczących COVID-19 i zespołu pokowidowego, dotychczas nie przeprowadzono wielu badań traktujących o mechanizmach pogorszenia tolerancji wysiłku w tych jednostkach chorobowych.

W badaniu opisanym w publikacji „Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction" wykazano, że mężczyźni mają dwukrotnie większe ryzyko ograniczonej tolerancji wysiłku fizycznego w zespole long COVID niż kobiety. Ponadto, na podstawie dokonanych analiz stwierdzono, że obniżenie wartości parametrów echokardiograficznych: fali A, TAPSE, GLPS oraz zwiększenie TBW% w organizmie mają wpływ na pogorszenie tolerancji wysiłku.

Dotychczas opublikowane wyniki badań sugerują, że to kobiety mają wyższe ryzyko wystąpienia objawów zespołu long COVID [40-42]. Do tej pory jednak brakuje wystarczających danych oceniających tolerancję wysiłku fizycznego po COVID-19 uwzględniających różnice między płciami.

Fala A w badaniu echokardiograficznym odzwierciedla późnorozkurczowy napływ mitralny powstały w wyniku skurczu przedsionków. Wartość fali A jest szczególnie istotna w kontekście diagnostyki zaburzeń funkcji rozkurczowej lewej komory (LV) [43]. Obecność tych zaburzeń u pacjentów po przebyciu COVID-19 znajduje potwierdzenie w literaturze. Szekely i wsp. wykazali, że po w wyniku infekcji dysfunkcja rozkurczowa LV występuje częściej niż dysfunkcja skurczowa [44].

TAPSE to istotny wskaźnik oceny funkcji skurczowej prawej komory (RV). Mierzy on ruch płaszczyzny pierścienia trójdzielnego podczas skurczu. Ma zastosowanie w diagnostyce niewydolności serca, a także chorób płuc. Wartość TAPSE < 17 mm świadczy o dysfunkcji skurczowej RV [45]. W badaniu Lassen i wsp. wykazano, że hospitalizowani pacjenci z COVID-19 prezentowali cechy dysfunkcji skurczowej RV, jednakże uległa ona normalizacji po 2 miesiącach od zachorowania [46]. Natomiast w innych badaniach opisano utrzymującą się dysfunkcję skurczową RV po 30 [47], a nawet 74 dniach od zachorowania [48].

Globalne podłużne szczytowe odkształcenie lewej komory (GLPS) jest znane jako parametr bardziej czuły i obiektywny niż frakcja wyrzutowa w ocenie nieprawidłowości lewej komory. Badania wykazały, że jednym z powikłań COVID-19 może być dysfunkcja

skurczowa lewej komory [44,49]. W przytoczonej powyżej pracy Lassen i wsp., funkcja skurczowa LV nie ulegała normalizacji po 2 miesiącach od przebycia COVID-19, w przeciwieństwie do RV [46]. W badaniu Brito i wsp. u pacjentów po przechorowaniu infekcji o ciężkim przebiegu zaobserwowano obniżone wartości GLPS [50].

W naszej analizie oceniono także stan nawodnienia uczestników przy użyciu metody bioimpedancji. W literaturze obecnie nie są dostępne badania traktujące o wpływie przewodnienia na pogorszenie tolerancji wysiłku po COVID-19. Natomiast Cornejo-Pareja i wsp. wykorzystali metodę bioimpedancji do oceny składu masy ciała pacjentów w trakcie COVID-19. Autorzy wykazali, że przewodnienie było jednym z czynników powodujących zwiększenie śmiertelności w tej grupie chorych [51].

W badaniu opisanym w artykule „Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction" analizowano użyteczność CPET u pacjentów z zespołem long COVID. W toku analiz potwierdzono, że CPET ma zastosowanie w tej grupie chorych. Wykazano, że FEV1/FVC% ≥ 103 jest najsilniejszym predyktorem w przewidywaniu objawów zespołu long COVID.

Stosunek natężonej objętości wydechowej pierwszosekundowej do natężonej pojemności życiowej (FEV1/FVC%) jest podstawowym parametrem oceny zaburzeń wentylacji [52]. Badania dotyczące pacjentów po COVID-19 potwierdzają długotrwałą obecność objawów ze strony układu oddechowego, a także odchyleń w spirometrii [53,54]. Lehmann i wsp. wykazali, że chorzy z objawami zespołu pokowidowego mieli obniżone wartości FVC, całkowitej pojemności płuc (ang. total lung capacity - TLC) oraz zdolności dyfuzyjnej płuc dla tlenku węgla (ang. diffusing capacity of the lungs for carbon monoxide – DLCO) [55].

Publikacja "Predictors of Long COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery" opisuje wyniki badania, w którym udowodniono, że zwiększone objętości lewej komory (EDV i ESV) oraz zawartość tłuszczu (FM) wiążą się z redukcją $VO_{2max}$ po 15 miesiącach od przechorowania COVID-19 (roczny follow-up).

Wpływ nadmiernej ilości tkanki tłuszczowej na zmniejszenie pochłaniania tlenu został potwierdzony w kilku badaniach [56,57]. Natomiast dane dotyczące objętości lewej komory kontrastują z wynikami dotychczas przeprowadzonych badań, w których

wykazano związek między zmniejszonymi wartościami EDV i ESV i objawami long COVID [58,59]. Należy zaznaczyć, że wyniki pochodzą z danych obserwacyjnych i konieczne są dalsze badania w tym zakresie.

Przedstawione analizy dowodzą, że COVID-19, a także zespół long COVID to istotny problem dla zdrowia publicznego. Pacjenci mogą doświadczać wielu objawów, które mogą mieć niekorzystny wpływ na jakość życia i funkcjonowanie w społeczeństwie. Wskazane jest prowadzenie dalszych badań na większej grupie chorych w celu opracowania odpowiednich strategii diagnostyczno-terapeutycznych.

### 6.6. Wnioski końcowe

1. Wykazano, że mężczyźni mają dwukrotnie większe ryzyko ograniczonej tolerancji wysiłku fizycznego w zespole long COVID niż kobiety.
2. W toku analiz jedno- i wieloczynnikowych udowodniono, że obniżone wartości parametrów echokardiograficznych: fali A, TAPSE, GLPS oraz zwiększenie TBW% są związane z pogorszeniem wydolności fizycznej u chorych po przebyciu COVID-19.
3. Za pomocą analizy krzywej ROC wykazano, że FEV1/FVC% ≥ 103 jest najsilniejszym predyktorem w przewidywaniu objawów zespołu long COVID.
4. Potwierdzono użyteczność badania spiroergometrycznego u pacjentów z zespołem long COVID.
5. Udowodniono, że zwiększone objętości lewej komory (EDV i ESV) oraz zawartość tłuszczu (FM) wiążą się z redukcją $VO_{2max}$ po 15 miesiącach od przechorowania COVID-19 (roczny follow-up).

### 6.7. Implikacje kliniczne

Przedstawione badanie miało na celu podkreślenie, jak istotnym problemem był i wciąż jest COVID-19. Wirus, który powoduje tę chorobę dotyka nie tylko układu oddechowego, ale ma również wpływ na układ krążenia. Objawy, które wywołuje mogą imitować objawy choroby układu sercowo-naczyniowego. Aby obrać właściwe postępowanie terapeutyczne, ważnym aspektem jest odpowiednia diagnostyka. Na podstawie powyższych analiz udowodniono, że badanie spiroergometryczne jest istotnym narzędziem nie tylko u pacjentów, którzy wymagają kwalifikacji do przeszczepu serca czy u sportowców, ale także u pacjentów, którzy przebyli zakażenie SARS-CoV-2.

Pozwala na zidentyfikowanie charakteru zgłaszanych objawów (tj. duszność, pogorszenie tolerancji wysiłku) i w związku z tym różnicowanie między zespołem long COVID oraz chorobami układu sercowo-naczyniowego. Wykonane badania mogą przyczynić się do wdrożenia nowych metod diagnostyczno-terapeutycznych oraz opracowania programów rehabilitacji u pacjentów po COVID-19 oraz z zespołem long COVID.

### 6.8. Ograniczenia badania

Przeprowadzone analizy mają pewne istotne ograniczenia. Pierwszym i krytycznym ograniczeniem jest fakt, że były to badania nierandomizowane, na małej grupie badanej, przeprowadzone w jednym ośrodku. Populacja pacjentów była ograniczona do polskich pacjentów hospitalizowanych w jednym Oddziale, co mogło zakłócić obserwację, ponieważ pacjenci kierowani do szpitala nie są reprezentatywni dla całej populacji pacjentów z zespołem long COVID. Istotnym ograniczeniem projektu jest także fakt, że nie analizowano wpływu przyjmowanych leków na badane parametry. Ponadto badanie obejmowało tylko pacjentów, u których można było przeprowadzić badanie spiroergometryczne. Nie oceniono także istotnych parametrów wymiany gazowej: TLC oraz DLCO. Badanie echokardiograficzne zostało przeprowadzone tylko w spoczynku.

Ze względu na wymienione ograniczenia, wyniki badania należy ostrożnie interpretować w odniesieniu do innych populacji. Pomimo to, atutem powyższych analiz jest fakt, że były to jedne z pierwszych badań traktujących o pogorszeniu tolerancji wysiłku po przebyciu COVID-19 oraz wykorzystaniu CPET w diagnostyce u chorych z zespołem long COVID. Przeprowadzono również szeroki panel innych badań, tj. diagnostykę laboratoryjną, echokardiograficzną, a także analizę składu ciała metodą bioimpedancji. Przedstawione wyniki pozwalają zidentyfikować czynniki przyczyniające się do pogorszenia wydolności fizycznej oraz podkreślają znaczenie długoterminowego monitorowania oraz leczenia osób z zespołem pokowidowym.

## 7. KOPIE OPUBLIKOWANYCH PRAC

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# Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction

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**Abstract:** Exercise intolerance de novo is one of the most common reported symptoms in patients recovering from the Coronavirus Disease 2019 (COVID-19). The present study determines etiological and pathophysiological factors influencing the mechanism of impaired exercise tolerance in patients during Long-COVID. Consequently, the factors affecting the percentage predicted oxygen uptake at peak exercise (%$VO_2$pred) in patients after COVID-19 with a normal left ventricular ejection fraction (LVEF) were assessment. A total of 120 patients recovering from COVID-19 at three to six months after confirmed diagnosis were included. The clinical examinations, laboratory test results, echocardiography, non-invasive body mass analysis, and spiroergometry were evaluated. The subjects were divided into the following groups: study patients' group with worsen oxygen uptake (%$VO_2$pred < 80%; $n = 47$) and control group presenting%$VO_2$pred ≥ 80% ($n = 73$). ClinicalTrials.gov Identifier: NCT04828629. The male gender and the percent of total body water content (TBW%) were significantly higher in the study group compared to the control group (53 vs. 29%, $p = 0.007$ and 52.67 (±6.41) vs. 49.89 (±4.59), $p = 0.02$; respectively). Patients with %$VO_2$pred < 80% presented significantly lower global peak systolic strain (GLPS), tricuspid annular plane systolic excursion (TAPSE), and late diastolic filling (A) velocity (19.34 (±1.72)% vs. 20.10 (±1.35)%, $p = 0.03$; 21.86 (±4.53) vs. 24.08 (±3.20) mm, $p = 0.002$ and median 59.5 (IQR: 50.0–71.0) vs. 70.5 (IQR: 62.0–80.0) cm/s, $p = 0.004$; respectively) compared to the controls. The results of the multiple logistic regression model show that (A) velocity (OR 0.40, 95%CI: 0.17–0.95; $p = 0.03$) and male gender (OR 2.52, 95%CI: 1.07–5.91; $p = 0.03$) were independently associated with %$VO_2$pred. Conclusions: Men have over twice the risk of persistent limited exercise tolerance in Long-COVID than women. The decreased (A) velocity, TAPSE, GLPS, and hydration status are connected with limited exercise tolerance after COVID-19 in patients with normal LVEF.

**Keywords:** COVID-19; exercise intolerance; global peak systolic strain; body mass compartments; personalization of body structure

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## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the coronavirus disease 2019 (COVID-19). The pandemic has spread all over the world since its first appearance in Wuhan (China) in December 2019 [1]. The SARS-CoV-2 infection has a full range of clinical manifestations from asymptomatic to dyspnea, fever, fatigue, dry cough, myalgias, and chest pain, as well as imaging and laboratory abnormalities, such as bilateral ground-glass opacities on chest CT scans and lymphopenia [2]. Pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and specific organ dysfunction may be other clinical presentations of COVID-19. The cardiovascular system can be also affected by COVID-19. SARS-CoV-2, through ACE2 (angiotensin-converting enzyme

2) as a receptor for the viral spike protein, can infect the heart, vascular tissues, and circulating cells [3]. This enzyme is a homologue of the angiotensin-converting enzyme (ACE) and plays an essential role in the renin–angiotensin–aldosterone system (RAAS), which involves blood pressure regulation and electrolyte homeostasis [4]. The spike protein plays a key role in the virus tissue tropism. This protein binds to the ACE2 receptor on the surface of the host cell. The binding blocks ACE2 activity and thus reduces the enzyme expression in the membrane [5]. The imbalance between ACE and ACE2 leads to an escalation in Ang II-mediated vasoconstriction and a decrease in Ang (1–7)-mediated vasodilation. Put simply, malfunctional RAAS may exaggerate the progression of COVID-19, especially during a cytokine release storm [6]. Cardiovascular cells that express ACE2 are possibly at risk for SARS-CoV-2 infection. Other factors, including expression of the host proteases that prime the virus, are required for infection as well [7]. The loss of ACE2 by SARS-CoV-2-induced internalization would be predicted to aggravate underlying cardiovascular disease (CVD) acutely and possibly in the long term. Acute cardiac injury is a common extrapulmonary manifestation of COVID-19 with possible chronic consequences. Post-acute sequelae of SARS-CoV-2 infection or long-COVID, can occur in recovering patients [8]. The clinical manifestations of cardiac involvement could range from an absolute lack of symptoms in the presence of elevated troponin levels, with or without ECG or imaging abnormalities; pulmonary embolism; acute coronary syndromes; myocarditis; acute heart failure to chronotropic incompetence; arrhythmia; and sudden cardiac death [9–11]. Frequent symptoms in patients who have recovered from COVID-19 also include dyspnea, fatigue, breathlessness, persistence of smell and taste disturbances, muscle aches, headaches, anxiety, sleep disturbances, and reduced exercise tolerance [12,13]. Exercise is determined by oxygen supply, oxygen uptake, and the clearance of toxic metabolites. These mechanisms are dependent on the pulmonary and cardiovascular systems to gain optimal exercise performance. Hence, there is an option to address the functional competence of the organs by coupling external adjustments to cellular respiration by studying external respiration in response to exercise [14]. The relevant tool to estimate the functional capacity during exercise is cardiopulmonary exercise testing (CPET). The main outcome of aerobic capacity is the peak oxygen uptake ($VO_2$peak), defined as the maximum amount of oxygen that can be absorbed during exercise. CPET is considered the gold standard for the assessment of physical fitness and evaluating the interaction of cardiovascular, respiratory, and metabolic systems. Cardiopulmonary evaluation can be conducted safely among non-hospitalized people affected by COVID-19 symptoms. Thus, we sought to quantify and describe the extent and the main mechanisms of exercise limitation in these patients.

The aim of the study was to identify the etiological and pathophysiological factors influencing the mechanism of exercise intolerance assessed in CPET, as well as biochemical and echocardiographic parameters in the COVID-19 survivors.

## 2. Materials and Methods

### 2.1. Basic Characteristics

We recruited 120 consecutive patients from the Department of Cardiology recovering from COVID-19 at three to six months after confirmed diagnosis in this study. The subjects were hospitalized in the Department of Cardiology and Congenital Heart Diseases of Adults between December 2020 and December 2021. There were no differences in medical treatment between the groups. All patients enrolled in this study performed CPET on the ergometer. The definition of %$VO_2$pred is a percentage predicted oxygen uptake at peak exercise $VO_2$. The patients were divided into a group that demonstrated worse oxygen uptake (%$VO_2$pred < 80%; $n$ = 47) at the median age of 49 years old (median $VO_2$max 17 mL/kg/min) and a control group at the median age of 55 years old who presented $VO_2$pred ≥ 80% (73 patients, median 23 mL/kg/min).

The exclusion criteria were as following: diagnosis of cardiomyopathy; diagnosis of heart failure—left ventricular ejection fraction (LVEF) < 50% and signs and symptoms of

heart failure or LVEF ≥ 50% with signs and symptoms and raised natriuretic peptides; unstable angina; unstable heart rhythm disorders; advanced atrioventricular block; acute pulmonary embolism; past myocardial infarction; uncontrollable arterial hypertension—systolic blood pressure ≥ 150 mmHg and/or diastolic blood pressure ≥ 100 mmHg; acute pericarditis or myocarditis; active endocarditis; intracerebral hemorrhage, transient ischemic attack and stroke in past medical history; chronic kidney disease (stage IV and V according to the National Kidney Foundation); severe hypo- and hyperthyroidism; active autoimmune disorder; recorded neoplastic process; taking cytostatic drugs, antiretroviral drugs, glucocorticosteroids, and immunosuppressants; blood transfusion within the last 6 months; documented bone marrow or other transplanted organs; active systemic infection; human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) carrier or positive for hepatitis B surface antigen (HBsAg) or antibodies to HCV; alcohol and drug abuse; pregnancy and lactation; severe injury or surgery in the last month; inability of the patient to collaborate and/or provide informed consent to participate in the study; physical disability preventing the performance of a cardiopulmonary exercise testing; and subjects who did not express their informed consent to participate in a research study.

The research was accepted by the Polish Mother's Memorial Hospital Research Institute (PMMHRI-BCO.75/2020), and it is in compliance with the Declaration of Helsinki.

### 2.2. Laboratory Tests

Blood samples were collected into polyethylene-terephthalate tubes from each patient. Laboratory tests were obtained following a minimum of 12 h after the last meal in the hospital laboratory. We measured renal function (creatinine, glomerular filtration rate (GFR) was estimated by Modification of Diet in Renal Disease (MDRD)) parameters and liver function (aspartate transaminase (ASP) and alanine aminotransferase (ALT)) parameters; lipoprotein profile: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC); glucose levels; inflammatory cytokine (C-reactive protein (CRP)); and hematology. Additionally, the measurement of N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) was performed.

### 2.3. Echocardiography

Echocardiograms were performed using the Vivid E95 system (GE Healthcare, Chicago, IL, USA). Quantitative measures were achieved in accordance with current guidelines [15]. The modified biplane Simpson's rule was necessary to measure left ventricular (LV) volume and ejection fraction (EF). Left atrial (LA) volume was estimated using the modified biplane Simpson's method from apical 2- and 4-chamber views at end-systole and was indexed to body surface area (LA volume index–LAVi) [16]. Other relevant analyzed parameters were maximal early (E) and late (A) transmitral velocities and the ratio of early to late diastolic transmitral flow velocity (E/A) [17]. We also assessed global peak systolic strain (GLPS) based on speckle tracking echocardiography. The right ventricular (RV) functional measures were tissue Doppler echocardiography (TDE) and tricuspid annular plane systolic excursion (TAPSE) [18].

### 2.4. Spiroergometry

The MetaSoft Studio application software from CORTEX systems was used for CPET. Subjects exercised by cycle ergometer Bike M (CORTEX Biophysik GmbH, Leipzig, Germany) with a metabolic gas analyzer METALYZER 3B (CORTEX Biophysik GmbH, Leipzig, Germany) [19]. Spirometry assessment was conducted before the activity. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC were measured. Additionally, we evaluated the forced expiratory flow over the middle of one half of the FVC (FEF 25–75). During exercise on a bicycle ergometer, oxygen saturation, electrocardiogram (ECG), blood pressure, and heart rate were monitored. Oxygen uptake is the necessary parameter in the interpretation of CPET. Oxygen uptake ($VO_2$) is calculated

from the difference between the volume of $O_2$ in the inhaled and exhaled air during exercise per unit of time and when the steady state is equal to the metabolic $O_2$ consumption. The definition of the $VO_2$ peak is the highest attainable $VO_2$ for a subject. Other measured CPET parameters include oxygen uptake at anaerobic threshold ($VO_2$AT), the minute ventilation/carbon dioxide production slope ($VE/VCO_2$ slope), and the respiratory exchange ratio (RER) [20].

### 2.5. Body Mass Analysis

The Segmental Body Composition Analyzer (Tanita Pro, Tokyo, Japan) is a tool to assess non-invasive body mass analysis. This equipment provides estimated values for each measured value using the dual-energy X-ray absorptiometry (DXA) method, estimated value for the total body water measured value by the dilution method and estimated value for the visceral fat using the Bioelectrical Impedance Analysis (BIA method). Subjects were asked to stand barefoot in a stable position. The device provided separate body mass readings for different segments of the body—legs, arms, and whole body—using an algorithm incorporating impedance, age, and height to estimate total and regional fat mass (FM) and fat-free mass (FFM) [21]. The following parameters were also obtained: extracellular water (ECW), intracellular water (ICW), and total body water (TBW). ECW pertains to all body fluid outside the cells. The ICW compartment is the system that includes all fluid enclosed in cells by their plasma membranes. TBW is the total amount of fluid in a person's body expressed as a percentage of their total weight. Additionally, we calculated the ECW/TBW% ratio [22].

### 2.6. Statistical Analysis

The analysis was obtained using the STATISTICA 13.1 software package (StatSoft, Cracow, Poland). The Shapiro–Wilk test assessed the normality of distribution. To compare two groups, the Student's *t*-test for continuous variables with normal distribution and Mann-Whitney U test for non-normally distributed variables were used. These categorical data were tested by backward stepwise multivariate logistic regression. In analyses, a $p$-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Evaluation of Basic Characteristics

We included 120 patients in this study. The subjects were divided into a group that demonstrated worse oxygen uptake ($\%VO_2pred < 80\%$; $n = 47$) at the median age 49 (IQR: 30–65) and a control group at the median age 55 (IQR: 47–64) who presented with $VO_2pred \geq 80\%$ (73 patients). The differences between age, height, body mass, body mass index (BMI), and body surface area (BSA) were not statistically significant between groups. Data are presented in Table 1.

### 3.2. Evaluation of Laboratory Tests

Subjects with $\%VO_2pred < 80\%$ presented decreased levels of total cholesterol in comparison to the control group. Statistically significant differences were not observed regarding other biochemical parameters. The results are shown in Table 1.

### 3.3. Evaluation of Echocardiography

The (A) velocity, GLPS, and TAPSE were significantly lower (median 59.5 (IQR: 50.0–71.0) vs. 70.5 (IQR: 62.0–80.0) cm/s, $p = 0.004$; 19.34 (±1.72)%vs. 20.10 (±1.35)%, $p = 0.03$; 21.86 (±4.53) vs. 24.08 (±3.2) mm, $p = 0.002$; respectively) in patients who presented with peak $VO_2 < 80\%$ compared to controls. In the study group, E/A was higher (median 1.23 (IQR: 0.98–1.70) vs. 1.01 (IQR: 0.80–1.22), $p = 0.006$) than in the control group. There were no statistically significant differences regarding EF, LA volume, LAVi, E, and TDE S' ($p = 0.44$; $p = 0.2$; $p = 0.32$; $p = 0.59$; $p = 0.17$; respectively). Data are presented in Table 1 and Figure 1.

**Table 1.** Evaluation of basic characteristics, laboratory tests, and echocardiography among the investigated groups.

| Parameter | Peak $VO_2$ < 80% $VO_2$ Predicted $n$ = 47 | Peak $VO_2$ ≥ 80% $VO_2$ Predicted $n$ = 73 | $p$ |
|---|---|---|---|
| Age | (30–65), 49 * | (47–64), 55 * | 0.08 |
| Height (cm) | (164–176), 170 * | (164–173), 169 * | 0.39 |
| Body mass (kg) | (65–89), 75 * | (69–89), 77 * | 0.51 |
| BMI (kg/m$^2$) | (22.70–29.98), 25.97 * | (24.61–30.49), 27.28 * | 0.07 |
| BSA (m$^2$) | (1.69–2.04), 1.86 * | (1.75–2.01), 1.85 * | 0.94 |
| hs-cTnT (pg/mL) | (3.70–9.85), 4.90 * | (3.0–6.9), 4.6 * | 0.14 |
| NT-proBNP (pg/mL) | (31–125), 73 * | (39–106), 73 * | 0.48 |
| Hemoglobin (g/dL) | (12.9–14.6), 13.9 * | (12.4–14.3), 13.3 * | 0.11 |
| Creatinine (mg/dL) | (0.65–0.90), 0.78 * | (0.66–0.88), 0.73 * | 0.27 |
| GFR (mL/min/1.73 m$^2$) | (79.9–107.7), 98.1 * | (79.0–98.7), 89.9 * | 0.07 |
| Glucose (mg/dL) | (86–99), 91 * | (86–93), 91 * | 0.44 |
| HDL cholesterol (mg/dL) | (35–58), 49 * | (42–59), 50 * | 0.38 |
| LDL cholesterol (mg/dL) | 92.29 (±34.64) | 100.00 (±29.72) | 0.20 |
| Triglycerides (mg/dL) | (76–164), 101 * | (90–158), 114 * | 0.28 |
| Total cholesterol (mg/dL) | 163.83 (±39.12) | 179.00 (±36.22) | 0.03 |
| ALT (U/L) | (15–25), 22 * | (17–35), 22 * | 0.25 |
| AST (U/L) | (24–29), 27 * | (24–32), 26 * | 0.47 |
| CRP (mg/L) | (0.5–0.5), 0.5 * | (0.5–0.5), 0.5 * | 0.66 |
| EF (%) | (55–66), 62 * | (59–66), 62 * | 0.44 |
| LA volume (mL) | (39.0–78.5), 52.0 * | (49–78), 61 * | 0.20 |
| LAVi (mL/m$^2$) | (21.9–39.5), 30.0 * | (27.0–39.3), 31.9 * | 0.32 |
| E (cm/s) | (61–87), 72 * | (60–83), 72 * | 0.59 |
| A (cm/s) | (50.0–71.0), 59.5 * | (62.0–80.0), 70.5 * | 0.004 |
| E/A | (0.98–1.70), 1.23 * | (0.80–1.22), 1.01 * | 0.006 |
| GLPS (%) | 19.34 (±1.72) | 20.10 (±1.35) | 0.03 |
| TAPSE (mm) | 21.86 (±4.53) | 24.08 (±3.2) | 0.002 |
| TDE S′ (cm/s) | (11–15), 14 * | (12–16), 14 * | 0.17 |

*—median; values with non-normal distributions are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). Peak $VO_2$—highest oxygen uptake ($VO_2$) during the maximal exercise; $VO_2$ predicted—percent predicted oxygen uptake at peak exercise; BMI—body mass index; BSA—body surface area; hs-cTnT—high-sensitivity cardiac troponin; NT-proBNP—N-terminal prohormone of brain natriuretic peptide; GFR—glomerular filtration rate; HDL—high-density lipoprotein; LDL—low-density lipoprotein; ALT—alanine aminotransferase; AST—aspartate aminotransferase; CRP—c-reactive protein; EF—left ventricular ejection fraction; LA—left atrium; LAVi—left atrial volume index; E—early diastolic filling velocity, A—late diastolic filling velocity; E/A—ratio of early to late diastolic transmitral flow velocity; GLPS—global peak systolic strain; TAPSE—tricuspid annular plane systolic excursion; TDE S′—tissue Doppler echocardiography.

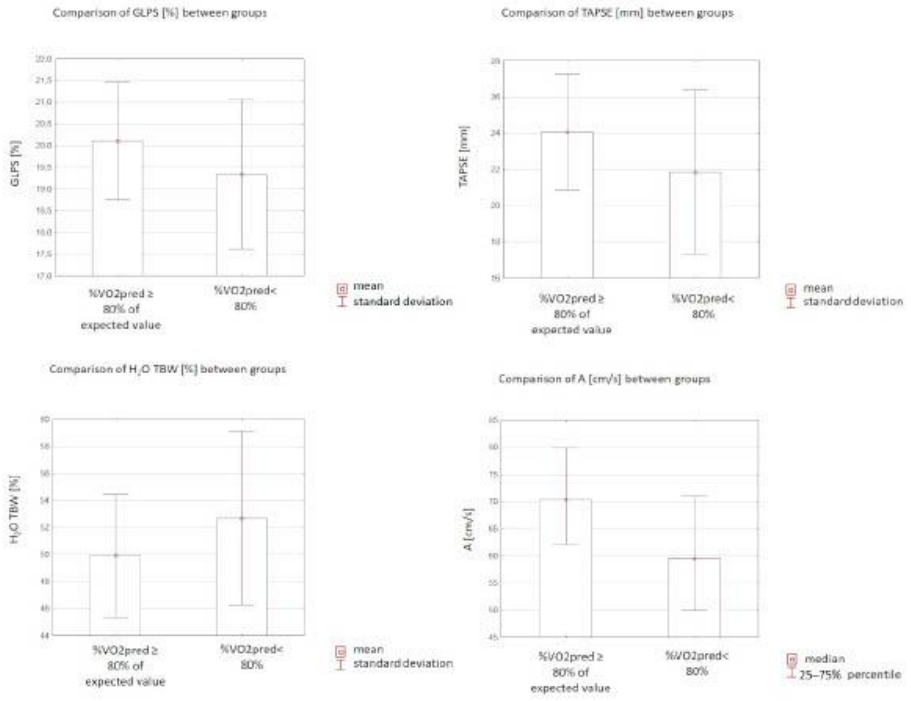


**Figure 1.** Comparison of selected echocardiographic and body mass analysis parameters between the investigated groups. %$VO_2$ pred—percentage predicted oxygen uptake at peak exercise; GLPS—global peak systolic strain; TAPSE—tricuspid annular plane systolic excursion; A—late diastolic filling velocity; $H_2O$ TBW—total body water.

### 3.4. Evaluation of Spiroergometry

Patients with worse oxygen consumption presented with significantly decreased HR max, peripheral SBP max, FVC%, and $VO_2$AT (132.87 (±33.61) vs. 146.63 (±20.46), $p = 0.006$; median 150 (IQR: 130–170) vs. 180 (IQR: 150–200) mmHg, $p < 0.0001$; 99.61 (±14.74) vs. 111.71 (±16.95) %, $p < 0.0001$; median 12 (IQR: 10–15) vs. 15 (IQR: 13–16) mL/min/kg, $p = 0.001$; respectively). In the study group, the FEF 25–75 was higher in comparison to the controls (3.25 (±1.23) vs. 2.66 (±1.13) L/s, $p = 0.01$). There were no significant differences concerning exercise time, peripheral DBP max, FEV1, FVC (L), FEV1/FVC, FEV1/FVC%, RER, or VE/$VCO_2$ slope ($p = 0.06$; $p = 0.29$; $p = 0.79$; $p = 0.62$; $p = 0.78$; $p = 0.57$; $p = 0.14$; $p = 0.54$; respectively). The results are presented in Table 2.

### 3.5. Evaluation of Body Mass Analysis

Considering body mass compartments, only the TBW level (%) was significantly larger in patients with peak $VO_2 \geq 80\%$ $VO_2$ predicted (52.67 (±6.41)% vs. 49.89 (±4.59)%, $p = 0.02$) compared to controls. Statistically significant differences in the remaining parameters (Fat (kg and %), FFM, TBW (kg), ECW, ICW, ECW/TBW) were not detected ($p = 0.1$; $p = 0.1$; $p = 0.82$; $p = 0.84$; $p = 0.96$; $p = 0.8$; $p = 0.34$; respectively). The data are shown in Table 2 and Figure 1.

Table 2. Evaluation of spiroergometry and body mass analysis among the investigated groups.

| Parameter | Peak $VO_2$ < 80% $VO_2$ Predicted $n = 47$ | Peak $VO_2 \geq 80\%$ $VO_2$ Predicted $n = 73$ | $p$ |
|---|---|---|---|
| Exercise time (s) | (378–642), 507 * | (439–697), 580 * | 0.06 |
| HR max | 132.87 (±33.61) | 146.63 (±20.46) | 0.006 |
| Peripheral SBP max (mmHg) | (130–170), 150 * | (150–200), 180 * | <0.0001 |
| Peripheral DBP max (mmHg) | (70–90), 80 * | (80–90), 80 * | 0.29 |
| FEV1 (L) | (2.55–3.64), 2.99 * | (2.59–3.54), 3.03 * | 0.79 |
| FVC (L) | 3.90 (±1.05) | 3.80 (±0.94) | 0.62 |
| FVC% | 99.61 (±14.74) | 111.71 (±16.95) | <0.0001 |
| FEV1/FVC | (76.0–87.0), 82.5 * | (77–86), 83 * | 0.78 |
| FEV1/FVC% | (96–110), 104 * | (97–110), 105 * | 0.57 |
| FEF 25–75 (L/s) | 3.25 (±1.23) | 2.66 (±1.13) | 0.01 |
| RER | (1.01–1.10), 1.08 * | (1.03–1.12), 1.09 * | 0.14 |
| $VO_{2max}$ (mL/min/kg) | (14–25), 17 * | (20–26), 23 * | <0.0001 |
| $VO_2AT$ (mL/min/kg) | (10–15), 12 * | (13–16), 15 * | 0.001 |
| Peak $VO_{2max}$ (L) | (0.98–1.71), 1.29 * | (1.42–2.08), 1.73 * | <0.0001 |
| VE/$VCO_2$ slope | (26.2–34.6), 29.6 * | (25.5–32.6), 29.5 * | 0.54 |
| Fat (%) | 28.46 (±7.75) | 30.92 (±5.47) | 0.1 |
| Fat (kg) | (15.7–28.4), 20.5 * | (18.6–29.8), 25.3 * | 0.1 |
| FFM (kg) | (47–59.1), 56.5 * | (47.3–63.5), 52.7 * | 0.82 |
| TBW (kg) | (34.2–44.0), 41.4 * | (33.7–45.3), 38.5 * | 0.84 |
| TBW (%) | 52.67 (±6.41) | 49.89 (±4.59) | 0.02 |
| ECW (kg) | (15.8–19.3), 18.0 * | (14.7–19.8), 17.2 * | (0.96) |
| ICW (kg) | (19.4–25.5), 24.1 * | (19.1–26.2), 21.7 * | 0.8 |
| ECW/TBW × 100% | 43.17 (±3.23) | 43.77 (±2.37) | 0.34 |

*—median; values with non-normal distributions are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). Peak $VO_2$—highest oxygen uptake ($VO_2$) during the maximal exercise; $VO_2$ predicted—percent predicted oxygen uptake at peak exercise; DBP—diastolic blood pressure; SBP—systolic blood pressure; FEV1—forced expiratory volume in one second; FVC—forced vital capacity; FEV1/FVC—ratio of forced expiratory volume in one second to forced vital capacity; FEF 25–75%—forced expiratory flow over the middle one half of the FVC; RER—respiratory exchange ratio; $VO_{2max}$—the maximum rate of oxygen consumption attainable during physical exertion per kilogram; $VO_2AT$—oxygen uptake at anaerobic threshold per kilogram; peak $VO_2$—highest respiratory oxygen uptake ($VO_2$) achieved by the subject during the maximal exercise; VE/$VCO_2$ slope—the minute ventilation/carbon dioxide production slope; FFM—fat-free body mass; TBW—total body water; ECW—extracellular water; ICW—intracellular water, ECW/TBW%—ratio of extracellular water to total body water.

### 3.6. Multivariate Analysis

Parameters with a $p$ value < 0.05 in the univariate analysis were entered into the multivariate analysis using the logistic regression analysis. In a multiple logistic regression model, the two factors were found to be significantly associated with %$VO_2$pred were as follows: (A) velocity (OR 0.4, 95%CI: 0.17–0.95; $p = 0.03$) and gender (OR 2.52, 95%CI: 1.07–5.91; $p = 0.03$).

## 4. Discussion

As far as we are aware, the present study is the first analysis of any connection between echocardiographic parameters, hydration status, and worse oxygen uptake in CPET in COVID-19 survivors during Long-COVID. Patients with %$VO_2$pred < 80% presented with significantly lower GLPS, TAPSE, and (A) velocity in comparison to controls. A indicates

late diastolic mitral flow due to atrial contraction. Peak (A) velocity is often considered a measure of LA function with normal values of 0.8 ± 0.2 m/s in young healthy individuals. Multiple studies have used this parameter as an index of LA function assessment [23]. The percent of TBW content was significantly higher in the study group compared to patients with $\%VO_2pred \geq 80\%$. The results of multiple logistic regression models independently associated with $\%VO_2pred$ were (A) velocity and male gender.

Oxygen consumption ($VO_2$), in addition to physical fitness levels measurement, is an indicator of disease severity in patients with heart failure, chronic obstructive pulmonary disease (COPD), restrictive pulmonary disease, and pulmonary hypertension [24]. Exercise intolerance is defined as an abnormally low $VO_2$. Viral toxicity, systemic inflammatory response, changes in the immune system, microvascular injury, fibroblast proliferation due to diffuse alveolar damage, medications, prolonged hospitalization, and stress are considered to be main hypotheses of reduced exercise capacity [25]. Several studies suggested that exercise intolerance could result from physical deconditioning. Motiejunaite et al. conducted a study in which 114 subjects after COVID-19 underwent CPET. During CPET, 75% of the patients had exercise impairment with decreased peak $VO_2$ values. The median peak $VO_2$ was 17.9 [26]. Decreased exercise tolerance might be associated with mitochondrial injury. Consequently, this phenomenon can lead to reduced energy production during cellular respiration for ATP formation.

The study of Baratto et al. revealed that COVID-19 patients at the time of hospital discharge presented with decreased arterial $O_2$ content, higher cardiac output (CO) at rest, and a lower arteriovenous $O_2$ difference compared to healthy controls. Additionally, in the study group, a lower muscle $O_2$ extraction in the absence of increased pulmonary artery pressure and pulmonary vascular resistance, justifying the reduced peak $VO_2$ during exercise, was observed [27]. Some preliminary research studies evaluated exercise tolerance and cardiopulmonary function in ambulatory patients with Long-COVID. Jimeno-Almazàn et al. investigated the association between spiroergometry parameters, echocardiographic parameters, and the severity of symptoms. The study showed that greater exercise tolerance was related to less severe dyspnea and fatigue. Persistent symptoms of Long-COVID were connected with worse fitness level [28]. In one randomized control trial, the authors conducted CPET in 39 participants with Long-COVID. The subjects were randomly divided into a group used to evaluate a tailored exercise program and the control group, which followed the WHO guidelines for rehabilitation after COVID-19. In both groups, improvement of the exercise capacity was observed. Additionally, the authors demonstrated that supervised, tailored exercise programs are more safe and effective in these cases [29]. Echocardiography is readily accessible and may be used to assess for functional cardiac injury. Our findings demonstrated that lower (A) velocity, TAPSE, and GLPS values are related to worse exercise capacity. Previous authors have considered the impact of COVID-19 on the cardiovascular system using transthoracic echocardiography. Tangen et al. enrolled 92 subjects hospitalized in Norway and assessed a TTE three months after infection [30]. All participants had preserved LVEF. A total of 6.5% of the patients presented reduced left ventricle GLS, with no other explanation. A total of 20% of the patients were hospitalized in the intensive care unit, three of them required mechanical ventilation. Another study with 80 adult participants with preserved LVEF demonstrated that 63% of the subjects had symptoms three months after recovery. A total of 25% presented with a decreased GLS, and 8% had a reduced RV GLS [31]. The meta-analysis of Tian et al. showed that lower TAPSE relates to poor COVID-19 disease outcomes [32]. Sex differences have been demonstrated in the acute phase of COVID-19. Males were found to be more vulnerable to developing a severe disease than females, but few studies have assessed sex differences in Long-COVID syndrome. Pelà et al. demonstrated that females were more symptomatic than males, not only in the acute phase but also at follow-up [33]. In another research study, the authors evaluated the predictors of Long-COVID in patients without comorbidities and observed significant differences relating to sex between women with Long-COVID and women without any symptoms after SARS-CoV-2 recovery [34]. However, there have been

no studies until now accessing objectively exercise tolerance after COVID-19. In our study, males had a higher risk of persistent limited exercise tolerance. BIA has been suggested as a simple, rapid method to assess changes in hydration status. One of the measured parameters is TBW, which consists of intracellular and extracellular water. In the study of Cornejo-Pareja et al., the authors discovered that overhydration was an important factor of COVID-19 mortality. The researchers enrolled 127 COVID-19 patients. In multivariate analysis, HR was 2.967 (95%CI, 1.459–6.032, $p = 0.001$) for hydration and 2.528 (95%CI, 1.664–3.843, $p = 0.001$) for ECW/TBW [35].

The strength of our study is that this is the first study to assess the etiological and pathophysiological factors influencing the mechanism of exercise intolerance assessed with spiroergometry, as well as the biochemical and echocardiographic parameters in the COVID-19 survivors. We are the first to demonstrate that the patients during Long-COVID without heart failure diagnosis, but with impaired exercise tolerance had worse function of the right ventricle, lower GLPS, LA function, and higher TBW. These findings, however, must be also seen in light of some limitations, including a relatively small study population (120 participants). It needs to be emphasized that it is an ongoing project, and these results need to be considered as preliminary. The study design was limited with regard to the evaluation of the possible effect of used medications. Furthermore, the study included only subjects who could perform CPET. In addition, transthoracic echocardiogram was assessed only at rest. Some echocardiographic parameters, such as left atrial strain, were not evaluated.

## 5. Conclusions

In conclusion, men have over twice the risk of persistent limited exercise tolerance after COVID-19 infection than women. Decreased (A) velocity, TAPSE, and worse GLPS and hydration status are associated with exercise intolerance after COVID-19 in patients with normal LVEF. Further studies are necessary to confirm our results.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Polish Mother's Memorial Hospital Research Institute (PMMHRI-BCO.75/2020).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Data Availability Statement:** Individual participant data that underlie the results reported in this article after deidentification (text, tables, figures, and appendices) as well as study protocol will be available for researchers who provide a methodologically sound proposal. Proposals may be submitted after 9 months and up to 36 months following the article's publication.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction

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**Abstract:** The emergence of the Coronavirus Disease 2019 (COVID-19) pandemic has brought forth various clinical manifestations and long-term complications, including a condition known as long COVID. Long COVID refers to a persistent set of symptoms that continue beyond the acute phase of the disease. This study investigated the risk factors and the utility of spiroergometry parameters for diagnosing patients with long COVID symptoms. The 146 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with normal left ventricular ejection fraction and without respiratory diseases were included and divided into two groups: the group demonstrating long COVID symptoms [n = 44] and the group without long COVID symptoms [n = 102]. The clinical examinations, laboratory test results, echocardiography, non-invasive body mass analysis, and spiroergometry were evaluated. ClinicalTrials.gov Identifier: NCT04828629. Patients with long COVID symptoms had significantly higher age [58 (vs.) 44 years; $p < 0.0001$], metabolic age [53 vs. 45 years; $p = 0.02$)], left atrial diameter (LA) [37 vs. 35 mm; $p = 0.04$], left ventricular mass index (LVMI) [83 vs. 74 g/m$^2$, $p = 0.04$], left diastolic filling velocity (A) [69 vs. 64 cm/s, $p = 0.01$], the ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion (E/E') [7.35 vs. 6.05; $p = 0.01$], and a lower ratio of early to late diastolic transmitral flow velocity (E/A) [1.05 vs. 1.31; $p = 0.01$] compared to the control group. In cardiopulmonary exercise testing (CPET), long COVID patients presented lower forced vital capacity (FVC) [3.6 vs. 4.3 L; $p < 0.0001$], maximal oxygen consumption measured during incremental exercise indexed per kilogram ($VO_{2max}$) [21 vs. 23 mL/min/kg; $p = 0.04$], respiratory exchange ratio (RER) [1.0 vs. 1.1; $p = 0.04$], forced expiratory volume in one second (FEV1) [2.90 vs. 3.25 L; $p = 0.04$], and a higher ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC%) [106 vs. 100%; $p = 0.0002$]. The laboratory results pointed out that patients with long COVID symptoms also had a lower rate of red blood cells (RBC) [4.4 vs. 4.6 $\times$ 10$^6$/uL; $p = 0.01$]; a higher level of glucose [92 vs. 90 mg/dL; $p = 0.03$]; a lower glomerular filtration rate (GFR) estimate by Modification of Diet in Renal Disease (MDRD) [88 vs. 95; $p = 0.03$]; and a higher level of hypersensitive cardiac Troponin T (hs-cTnT) [6.1 vs. 3.9 pg/mL; $p = 0.04$]. On the multivariate model, only FEV1/FVC% (OR 6.27, 95% CI: 2.64–14.86; $p < 0.001$) independently predicted the long COVID symptoms. Using the ROC analysis, the FEV1/FVC% $\geq$ 103 was the most powerful predictor of spiroergometry parameters (0.67 sensitive, 0.71 specific, AUC of 0.73; $p < 0.001$) in predicting the symptoms of long COVID. Spiroergometry parameters are useful in diagnosing long COVID and differentiating it from cardiovascular disease.

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**Keywords:** COVID-19; long COVID syndrome; exercise intolerance; body mass compartments

## 1. Introduction

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease, named Coronavirus Disease 2019 (COVID-19), which threatens human health and public safety. At the end of 2019, a novel coronavirus designated SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia [1]. The World Health Organization declared COVID-19 a pandemic in March 2020 [2]. Symptoms include coughing, fever, and shortness of breath. Common symptoms are fever, cough, sore throat, dyspnea, smell and taste disturbances, weakness, malaise, and muscle pain [3]. The SARS-CoV-2 infection is not limited to the respiratory system. It may trigger an excessive immune response known as a cytokine storm, which can lead to multiple organ failure and death [4]. Cardiovascular complications can be a significant contributor to the mortality associated with this disease. The mechanisms of cardiovascular injury caused by SARS-CoV-2 infection have not been fully elucidated, but it is speculated that SARS-CoV-2 affects the cardiovascular system through multiple mechanisms, including direct injury, downregulation of angiotensin-converting enzyme 2 (ACE2), immune injury, hypoxia injury, and psychological injury [5]. Patients with COVID-19 can present with dyspnea, chest pain, arrhythmias, and acute myocardial injury [6]. Studies have estimated that 4.5% to 36.6% of all COVID-19 patients continue to suffer from symptoms more than 3 months post-infection [7]. This condition is defined as long COVID syndrome [8]. The analysis of 153.760 individuals in national healthcare databases from the US Department of Veterans Affairs, with comparison to over 10 million contemporary and historical controls, reported an important expansion in the incidence of cardiovascular disease in surviving patients and a 55% increase in combined cardiovascular outcome 1 year after COVID-19. Additionally, increased risk was observed even in non-hospitalized patients, with risk related to the severity of the acute infection [9]. Dyspnea, fatigue, chest pain, muscle pain, cognitive impairment, taste and smell disturbances, and exercise intolerance are the most frequent symptoms of long COVID. Exercise capacity is defined as the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle. It is determined by pulmonary gas exchange, cardiovascular performance, and skeletal muscle metabolism [10]. Cardiopulmonary exercise testing (CPET) provides an evaluation of exercise capacity and assessment of integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems [11]. Therefore, we sought to determine the utility of CPET parameters in differentially diagnosing patients with long COVID syndrome.

The aim of this study was to investigate the risk factors and assess the utility of spiroergometry parameters in differentially diagnosing patients presenting symptoms (dyspnea, fatigue, pain in the chest, muscle pain, cognitive impairment, taste, and smell disturbances) persisting for a few months after recovery from SARS-CoV-2 infection (symptoms of long COVID).

## 2. Materials and Methods

### 2.1. Basic Characteristics

From the Department of Cardiology, 146 consecutive patients recovering from SARS-CoV-2 infection three to six months after a confirmed diagnosis were recruited for this study. Patient inclusion in the analysis was performed based on the existence of the exclusion criteria at the study start (three to six months after infection). A random sample from the electronic medical record was reviewed independently and in duplicate to validate the research strategy. The subjects were hospitalized in the Department of Cardiology and Congenital Heart Diseases of Adults between December 2020 and December 2021. The

subjects were divided into the two following groups: the group demonstrating long COVID symptoms (i.e., suffering from one of the following: dyspnea, fatigue, pain in the chest, muscle pain, cognitive impairment, taste or smell disturbances) [n = 44] and the group without long COVID symptoms [n = 102]. There were no differences between groups in pharmacological treatment. All subjects gave written informed consent to participate in this study. Patients performed CPET on the ergometer. The exclusion criteria were as following: unstable arterial hypertension; unstable angina; acute pulmonary embolism; diagnosis of heart failure or typical symptomatic heart failure; left ventricular ejection fraction (LVEF) < 50%; past myocardial infarction; unstable heart rhythm disorders; acute myocarditis or pericarditis; active endocarditis; advanced atrioventricular block; diagnosed cardiomyopathy (hypertrophic, dilated, restrictive, postpartum, tachyarrhythmic); stroke, transient ischemic attack, history of intracerebral bleeding; severe hyper- and hypothyroidism; pregnancy or lactation; chronic kidney disease (stage IV and V according to the National Kidney Foundation) and dialysis treatment; documented neoplastic process; the patient's inability to cooperate and/or give informed consent to participate in a research; alcohol and drug abuse; active autoimmune disease; taking immunosuppressants, cytostatic drugs, glucocorticosteroids, or antiretroviral drugs; a history of bone marrow or other organ transplant; treatment with blood products within the last 6 months; active systemic infection; hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) carrier or positive for hepatitis B surface antigen (HBsAg) or antibodies to HCV; surgery or a serious injury in the last month; physical disability that prevents the performance of a spiroergometric test; patients who did not express their informed consent to participate in this study.

This study is in compliance with the Declaration of Helsinki and was approved by the Polish Mother's Memorial Hospital Research Institute (PMMHRI-BCO.75/2020).

### 2.2. Laboratory Tests

Diagnostic blood samples were collected from each patient. The samples were obtained by needle puncture and withdrawn by suction through the needle into a vacuum blood collection system. Laboratory tests were performed in the hospital laboratory following a minimum 12-h period after the last meal. Routine laboratory tests included liver function [the alanine aminotransferase (ALT) and aspartate transaminase (ASP)] parameters and renal function [creatinine, glomerular filtration rate (GFR) estimate by Modification of Diet in Renal Disease (MDRD)] parameters, urea level, serum natrium (Na) and potassium (K) level, C-reactive protein (CRP), glucose level, lipoprotein profile: total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG), haematology, and D-dimer. In addition, the analysis of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) was conducted.

### 2.3. Echocardiography

The patients underwent transthoracic echocardiography (TTE) using the Vivid E95 system (GE Healthcare, Chicago, IL, USA). Quantitative measures were performed in accordance with current guidelines [12]. We calculated left ventricular dimensions in the end diastole: left ventricular internal diameter (LVID d), interventricular septum (IVS d), and left ventricular posterior wall (LVPW d). Left ventricular volume (LV) and ejection fraction (EF) were measured by the quantitative 2-dimensional biplane modified Simpson method from a 4- and 2-chamber view. The 2-dimensional maximal left atrial volume (LAV) was determined based on the apical 2- and 4-chamber views at end-systole without foreshortening, using a biplane modified Simpson's method excluding the LA appendage and pulmonary vein confluences [13]. Each LAV was indexed by body surface area (LAVi). The LV mass index (LVMI) was calculated by dividing the LV mass (in grams) by a body size variable, such as body surface area. Residual echocardiographic parameters analyzed were: maximal early (E) and late (A) transmitral velocities; ratio of early transmitral peak velocity to early diastolic peak annular velocity (E/E′); ratio of early to late diastolic transmitral flow

velocity (E/A); and deceleration time (Dec) and acceleration time (Ats). Global peak systolic strain (GLPS) was obtained using speckle-tracking echocardiography [14]. We also assessed the ascending aorta (AA), aortic bulb (AB), main pulmonary artery (MPA), and inferior vena cava (IVC) diameters. The right ventricular (RV) functional measure was tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler echocardiography (TDE) [15]. Additionally, we obtained the right atrial volume (RA) and distal right ventricular outflow tract (RVOT d).

### 2.4. Spiroergometry

Symptom-limited cardiopulmonary exercise testing (CPET) was performed on an electromagnetically braked upright cycle ergometer, Bike M (CORTEX Biophysik GmbH, Leipzig, Germany), with a metabolic gas analyzer, METALYZER 3B (CORTEX Biophysik GmbH, Leipzig, Germany), using the MetaSoft Studio application software of CORTEX systems. Prior to exercise, basic spirometry was performed. We recorded forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). Additionally, the FEV1/FVC ratio (Tiffeneau index) was obtained. Additionally, we evaluated forced expiratory flow over the middle half of the FVC (FEF 25–75) [16,17]. CPET on a bicycle ergometer was conducted with an additional continuous 12-lead electrocardiogram (ECG), heart rate (HR), oxygen saturation ($SpO_2$), and non-invasive blood pressure (NIBP) monitoring. The following parameters are important in the interpretation of CPET. Oxygen uptake ($VO_2$) is calculated from the difference between the volume of $O_2$ in the inhaled and exhaled air during exercise per unit of time, and in a steady state, it is equal to metabolic $O_2$ consumption. Peak $VO_{2max}$ represents the highest attainable $VO_2$ for a subject [18]. We also assessed other valuable CPET parameters. These derived measurements include respiratory exchange ratio (RER), oxygen uptake at anaerobic threshold ($VO_2$AT), and the minute ventilation/carbon dioxide production slope ($VE/VCO_2$ slope) [19].

### 2.5. Body Mass Analysis

The Segmental Body Composition Analyzer (Tanita Pro, Tokyo, Japan) is a device for non-invasive body mass analysis. This equipment provides estimated values for each measured value by the Dual-energy X-ray absorptiometry (DXA) method, an estimated value for the total body water measured value by the dilution method, and an estimated value for the visceral fat rating by the Magnetic Resonance Imaging (MRI) method using the Bioelectrical Impedance Analysis (BIA) method [20]. After gender, age, and height information had been entered into the device, participants were asked to stand barefoot in a stable position. The analyzer provides separate mass readings for different segments of the body and estimates total and regional fat mass (FM) and fat-free mass (FFM). Additionally, total body water (TBW), intracellular water (ICW), and extracellular water (ECW) were measured. Additionally, we examined the association between ECW/TBW, defined as the ECW/TBW% ratio, and basal metabolic rate (BMR) [21].

### 2.6. Statistical Analysis

The STATISTICA 13.1 software package (StatSoft, Cracow, Poland) was used for analysis. The concordance of the normal distribution of all variables was calculated with the Shapiro–Wilk test. To compare the 2 groups, the Student's *t*-test for continuous variables with a normal distribution and the Mann–Whitney U test for non-normally distributed variables were used. Predictors of the long COVID symptoms were identified using univariate analysis and the multivariate logistic regression method. The receiver operating characteristic (ROC) analyses were performed, and the sensitivity and specificity were determined. To reduce the bias with age between the long COVID group and the non-long COVID population, one-to-one nearest-neighbor propensity score matching was used. The parameters that met the following criteria: (1) they were statistically significant in univariate analysis and (2) the area under the ROC curve (AUC) was at least 0.630 were qualified for the multivariate model. Only the 6 parameters met both criteria, i.e., age, metabolic

age, A, E/A, E/E', and FEV1/FVC%. For these parameters, the cut-off points based on the Youdan index of the ROC curve were determined, i.e., age < 54 [years], metabolic age < 49 [years], A < 68 [cm/s], E/A < 1.3, E/E' < 7.15, and FEV1/FVC% > 103. As the correlations between A [cm/s] and E/A as well as between A [cm/s] and E/E' were observed (R spearman = −0.54; $p < 0.0001$ and R spearman = 0.34; $p = 0.002$, respectively), in the multivariable analysis only age < 54 [years], metabolic age < 49 [years], A < 68 [cm/s], and FEV1/FVC% > 103 were included. The results for the chosen parameters were transformed into dichotomous variables based on the Youden point. A chi-square test was used to compare dichotomous variables between the groups. In analyses, a $p$-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Evaluation of Basic Characteristics

In this study, 146 consecutive patients were enrolled. The subjects were divided into two groups: the group demonstrating long COVID symptoms [n = 44] and the group without long COVID symptoms [n = 102]. Subjects in this study group had significantly higher ages [median 58.0 (IQR: 48.0–67.0) vs. 44.5 (IQR: 31.0–53.0), $p < 0.0001$]. Statistically significant differences were not observed regarding body mass index (BMI), body surface area (BSA), systolic and diastolic blood pressure (SBP and DBP), and heart rate (HR). The data are presented in Table 1.

**Table 1.** Evaluation of basic characteristics among the investigated groups.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | $p$ |
|---|---|---|---|
| Basic characteristics | | | |
| Male sex | 41% | 36% | 0.26 |
| Age | (48.00–67.00), 58.00 * | (31.00–53.00), 44.50 * | <0.0001 |
| BMI (kg/m$^2$) | (23.90–31.12), 27.11 * | (23.85–31.16), 26.50 * | 0.62 |
| BSA (m$^2$) | (1.73–2.01), 1.86 * | (1.78–2.11), 1.91 * | 0.35 |
| SBP (mmHg) | (124.00–140.00), 130.00 * | (125.50–147.00), 134.50 * | 0.15 |
| DBP (mmHg) | (76.00–88.00), 80.00 * | (74.00–90.00), 85.50 * | 0.26 |
| HR | (70.00–80.00), 72.00 * | (68.00–83.50), 73.50 * | 0.90 |
| HA | 54% | 46% | 0.80 |
| Dyslipidemia | 52% | 48% | 0.40 |
| DM 2 | 31% | 69% | 0.21 |
| Nicotinism | 37% | 63% | 0.78 |
| Obesity | 55% | 45% | 0.75 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). BMI—body mass index; BSA—body surface area; SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate; HA—arterial hypertension; DM 2—type 2 diabetes mellitus.

### 3.2. Evaluation of Laboratory Tests

Patients with symptoms presented with higher levels of hs-cTnT [median 6.10 (IQR: 3.20–9.00) vs. 3.90 (IQR: 3.00–6.20) pg/mL, $p = 0.04$] and glucose [median 91.50 (IQR: 86.00–99.00) vs. 90.00 (84.50–93.00) mg/dL, $p = 0.03$] in comparison to controls. Red blood cell (RBC) concentration and GFR were lower in the study group compared to patients without symptoms [median 4.42 (IQR: 4.13–4.80) vs. 4.62 (IQR: 4.32–5.08) $10^6$/uL, $p = 0.01$; median 88.25 (IQR: 76.10–98.80) vs. 94.90 (IQR: 81.80–111.30) mL/min/1.73 m$^2$, $p = 0.03$, respectively]. Statistically significant differences were not observed regarding other biochemical parameters. We showed the results in Table 2.

**Table 2.** Evaluation of laboratory tests among the investigated groups.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | p |
|---|---|---|---|
| Laboratory tests | | | |
| hs-cTnT (pg/mL) | (3.20–9.00), 6.10 * | (3.00–6.20), 3.90 * | 0.04 |
| NT-proBNP (pg/mL) | (42.00–125.00), 86.00 * | (29.00–123.00), 61.00 * | 0.051 |
| RBC ($10^6$/uL) | (4.13–4.80), 4.42 * | (4.32–5.08), 4.62 * | 0.01 |
| Hemoglobin (g/dL) | (12.60–14.50), 13.30 * | (13.00–15.30), 13.90 * | 0.07 |
| PLT ($10^3$/uL) | 218.87 (±54.59) | 223.11 (±54.56) | 0.67 |
| Creatinine (mg/dL) | (0.67–0.89), 0.79 * | (0.66–0.90), 0.77 * | 0.87 |
| GFR (mL/min/1.73 $m^2$) | (76.10–98.80), 88.25 * | (81.80–111.30), 94.90 * | 0.03 |
| Urea (mg/dL) | 35.24 (±11.26) | 31.75 (±9.36) | 0.07 |
| Glucose (mg/dL) | (86.00–99.00), 91.50 * | (84.50–93.00), 90.00 * | 0.03 |
| ALT (U/L) | (18.00–29.00), 22.50 * | (14.50–34.00), 23.00 * | 0.93 |
| ASP (U/L) | (24.00–30.00), 26.50 * | (23.50–38.00), 27 * | 0.37 |
| CRP (mg/dL) | (0.50–0.50), 0.50 * | (0.50–0.50), 0.50 * | 0.82 |
| D-dimer (ng/mL) | (186.00–450.00), 279.00 * | (197.00–439.00), 276.00 * | 0.82 |
| TC (mg/dL) | 171.32 (±40.71) | 173.55 (±45.88) | 0.77 |
| LDL (mg/dL) | 94.54 (±34.86) | 96.80 (±29.01) | 0.71 |
| HDL (mg/dL) | (40.00–58.00), 49.50 * | (36.00–59.50), 50.50 * | 0.99 |
| TG (mg/dL) | (86.00–163.00), 111.50 * | (80.00–150.00), 101.00 * | 0.57 |
| Na (mmol/L) | (138.00–140.00), 139.00 * | (137.50–140.00), 139.00 * | 0.20 |
| K (mmol/L) | (4.20–4.60), 4.30 * | (4.10–4.55), 4.30 * | 0.74 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). hs-cTnT—high-sensitivity cardiac troponin; NT-proBNP—N-terminal prohormone of brain natriuretic peptide; RBC—red blood cells; PLT—thrombocytes; GFR—glomerular filtration rate; ALT—alanine aminotransferase; AST—aspartate aminotransferase; CRP—c-reactive protein; TC—total cholesterol; LDL—low-density lipoprotein; HDL—high-density lipoprotein; TG—triglycerides; Na—serum natrium; K—serum potassium.

### 3.3. Evaluation of Echocardiography

Subjects with symptoms presented with higher LA, LVMI, A velocity, and E/E' [median 37.00 (IQR: 34.00–42.00) vs. 35.00 (IQR: 32.00–39.00) mm, $p = 0.04$; median 83.00 (IQR: 71.00–98.00) vs. 74.00 (IQR: 61.00–98.00) g/$m^2$, $p = 0.04$; median 69.00 (IQR: 60.00–83.00) vs. 64.00 (IQR: 51.00–74.00) cm/s, $p = 0.01$; median 7.35 (IQR: 6.00–8.95) vs. 6.05 (IQR: 5.50–7.10), $p = 0.01$, respectively] compared to control group. E/A was decreased in the study group [median 1.05 (IQR: 0.80–1.22) vs. 1.31 (0.95–1.67), $p = 0.01$] in comparison to patients without symptoms. We did not observe statistically significant differences regarding other echocardiographic parameters. Table 3 contains the attached data.

**Table 3.** Evaluation of selected echocardiographic parameters among the investigated groups.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | p |
|---|---|---|---|
| Echocardiography | | | |
| LVID d (mm) | (45.00–53.00), 48.00 * | (43.00–53.00), 46.00 * | 0.16 |
| IVS d (mm) | (9.00–11.00), 10.00 * | (9.00–11.00), 9.00 * | 0.76 |
| LVPW d (mm) | (8.00–10.00), 9.00 * | (8.00–10.00), 9.00 * | 0.75 |
| LA (mm) | (34.00–42.00), 37.00 * | (32.00–39.00), 35.00 * | 0.04 |
| LAV (mL) | (47.00–81.00), 63.00 * | (41.50–73.00), 53.50 * | 0.23 |
| LAVi (mL/$m^2$) | (26.55–40.98), 33.30 * | (23.00–38.10), 28.65 * | 0.10 |
| RA ($cm^2$) | (13.50–18.50), 16.10 * | (13.00–20.00), 16.15 * | 0.86 |
| RVOT d (mm) | 31.45 (±4.38) | 30.57 (±4.87) | 0.30 |
| AB (mm) | (30.00–36.00), 32 * | (30.00–37.00), 33.00 * | 0.97 |
| AA (mm) | (29.00–36.00), 32.00 * | (28.00–36.00), 31.00 * | 0.56 |
| MPA (mm) | (18.00–21.00), 19.50 * | (18.00–21.00), 19.00 * | 0.78 |
| IVC (mm) | (4.50–9.00), 6.50 * | (4.00–10.00), 6.00 * | 0.79 |
| LVMI (g/$m^2$) | (71.00–98.00), 83.00 * | (61.00–98.00), 74.00 * | 0.04 |

Table 3. *Cont.*

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | p |
|---|---|---|---|
| LVEF (%) | (56.00–65.00), 62.00 * | (59.00–67.00), 62.00 * | 0.37 |
| EDV ($cm^3$) | (71.00–103.00), 89.00 * | (75.00–105.00), 89.50 * | 0.88 |
| ESV ($cm^3$) | (25.00–42.00), 34.00 * | (25.00–44.00), 33.00 * | 0.79 |
| TAPSE (mm) | 23.31 (±3.83) | 22.83 (±3.98) | 0.50 |
| TDE S' (cm/s) | (12.00–16.00), 14.00 * | (12.00–15.00), 13 * | 0.10 |
| GLPS (%) | 19.68 (±1.91) | 19.90 (±1.96) | 0.62 |
| E (cm/s) | (63.00–85.00), 72.00 * | (60.00–90.00), 79.00 * | 0.49 |
| A (cm/s) | (60.00–83.00), 69.00 * | (51.00–74.00), 64.00 * | 0.01 |
| E/A | (0.80–1.22), 1.05 * | (0.95–1.67), 1.31 * | 0.01 |
| E/E' | (6.00–8.95), 7.35 * | (5.50–7.10), 6.05 * | 0.01 |
| Dec (ms) | (167.00–245.00), 205.00 * | (175.00–239.00), 194.00 * | 0.79 |
| Ats (ms) | (114.00–145.00), 133.00 * | (118.00–145.00), 133 * | 0.68 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). LVID d—left ventricular internal diameter end diastole; IVS d—interventricular septum end diastole; LVPW d—left ventricular posterior wall end diastole; LA—left atrial diameter; LAV—left atrial volume; LAVi—left atrial volume index; RA—right atrial area; RVOT—distal right ventricular outflow tract; AB—aortic bulb; AA—ascending aorta; MPA—main pulmonary artery; IVC—inferior vena cava; LVMI—left ventricular mass index; LVEF—left ventricular ejection fraction; EDV—end-diastolic volume; ESV—end-systolic volume; TAPSE—tricuspid annular plane systolic excursion; TDE S'—tissue Doppler echocardiography; GLPS—global peak systolic strain; E—early diastolic filling velocity; A—late diastolic filling velocity; E/A—ratio of early to late diastolic transmitral flow velocity; E/E'—ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; Dec—deceleration time; Ats—acceleration time.

### 3.4. Evaluation of Spiroergometry

HR max and FEV1/FVC (%) were statistically greater in the study group [146.63 (±20.46) vs. 132.87 (±33.61), $p = 0.006$; median 106.50 (IQR: 99.00–112.00) vs. 100.00 (IQR: 90.00–105.00)%, $p = 0.0002$, respectively] compared to controls. Patients with symptoms also had lower FEV1, FVC (L), RER, and $VO_{2max}$ than subjects without symptoms [median 2.90 (IQR: 2.55–3.54) vs. 3.25 (IQR: 2.79–3.71) L, $p = 0.04$; 3.65 (±0.89) vs. 4.32 (±1.02) L, $p < 0.0001$; median 1.08 (IQR: 1.01–1.11) vs. 1.10 (IQR: 1.05–1.12), $p = 0.04$; median 21.00 (IQR: 16.00–25.00) vs. 23.00 (IQR: 19.00–29.00) mL/min/kg, $p = 0.04$, respectively]. There were no significant differences between exercise time, level of effort, SBP and DBP max, FVC (%), FEV1/FVC, FEF 25–75, $VO_2$AT, peak $VO_{2max}$, and VE/$VCO_2$ slope [$p > 0.05$ for all]. The spiroergometry parameters predicted long COVID-19 symptoms, with FEV1/FVC% ≥ 103 as the strongest predictor (0.67 sensitive, 0.71 specific, with an AUC of 0.73; $p < 0.001$, Figure 1). Results are shown in Table 4 and Figure 1.

Table 4. Evaluation of spiroergometry among the investigated groups.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | p |
|---|---|---|---|
| | Spiroergometry | | |
| Exercise time (s) | (384.00–662.00), 512.50 * | (412.00–719.00), 559.00 * | 0.38 |
| Level of effort (Wat) | (100.00–150.00), 125.00 * | (100.00–171.00), 125.00 * | 0.59 |
| HR max | 146.63 (±20.46) | 132.87 (±33.61) | 0.006 |
| Peripheral SBP max (mmHg) | (140.00–190.00), 160.00 * | (140.00–195.00), 160.00 * | 0.38 |
| Peripheral DBP max (mmHg) | (70.00–90.00), 80.00 * | (75.00–90.00), 80 * | 0.86 |
| FEV1 (L) | (2.55–3.54), 2.90 * | (2.79–3.71), 3.25 * | 0.04 |
| FVC (L) | 3.65 (±0.89) | 4.32 (±1.02) | <0.0001 |
| FVC (%) | 106.45 (±17.83) | 107.00 (±15.27) | 0.88 |
| FEV1/FVC | (77.00–88.00), 83.00 * | (74.00–85.00), 80.00 * | 0.051 |
| FEV1/FVC (%) | (99.00–112.00), 106.50 * | (90.00–105.00), 100.00 * | 0.0002 |
| FEF 25–75 (L/s) | 2.79 (±1.27) | 3.17 (±0.98) | 0.14 |
| RER | (1.01–1.11), 1.08 * | (1.05–1.12), 1.10 * | 0.04 |
| $VO_{2max}$ (mL/min/kg) | (16.00–25.00), 21.00 * | (19.00–29.00), 23.00 * | 0.04 |

Table 4. *Cont.*

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | *p* |
|---|---|---|---|
| $VO_2AT$ (mL/min/kg) | (11.00–17.00), 14.00 * | (13.00–20.00), 15.50 * | 0.07 |
| Peak $VO_{2max}$ (L) | (1.29–1.90), 1.58 * | (1.38–2.23), 1.77 * | 0.07 |
| $VE/VCO_2$ slope | (26.10–33.90), 29.70 * | (25.40–32.00), 28.05 * | 0.26 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). FEV1—forced expiratory volume in one second; FVC—forced vital capacity; FEV1/FVC—ratio of forced expiratory volume in one second to forced vital capacity; FEF 25–75%—forced expiratory flow over the middle one half of the FVC; RER—respiratory exchange ratio; $VO_{2max}$—the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise; $VO_2AT$—oxygen uptake at anaerobic threshold per kilogram; peak $VO_2$—highest respiratory oxygen uptake ($VO_2$) achieved by the subject during the maximal exercise; $VE/VCO_2$ slope—the minute ventilation/carbon dioxide production slope.

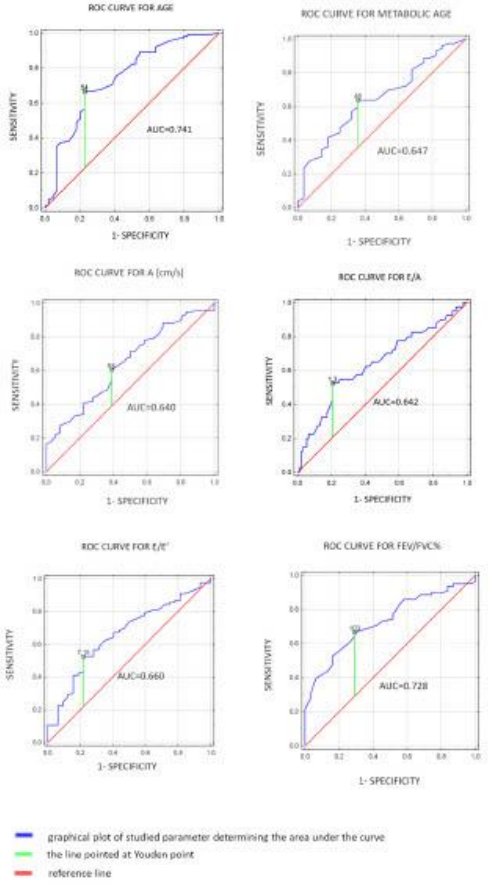


**Figure 1.** Receiver operating characteristic curves (ROC) for spiroergometric parameters in patients with long COVID symptoms. A—late diastolic filling velocity; E/A—ratio of early to late diastolic transmitral flow velocity; E/E'—ratio of peak velocity of early diastolic transmitral flow to peak velocity of early diastolic mitral annular motion as determined by pulsed wave Doppler; FEV1/FVC—ratio of forced expiratory volume in one second to forced vital capacity.

### 3.5. Evaluation of Body Mass Analysis

Regarding body mass analysis, only metabolic age was significantly higher in patients with symptoms [53.81 (±15.24) vs. 45.68 (±15.48), $p = 0.02$] in comparison to controls. Statistically significant differences between Fat (%), Fat (kg), FFM, TBW (kg), TBW (%), ECW, ICW, ECW/TBW × 100%, and BMR were not detected [$p > 0.05$, for all]. The results are listed in Table 5.

**Table 5.** Evaluation of body mass analysis among the investigated groups.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | p |
|---|---|---|---|
| | Body mass analysis | | |
| Fat (%) | 30.00 (±6.40) | 30.21 (±7.69) | 0.89 |
| Fat (kg) | (17.40–29.10), 23.50 * | (19.50–33.95), 24.70 * | 0.44 |
| FFM (kg) | (47.40–60.40), 53.60 * | (47.50–65.50), 56.65 * | 0.29 |
| TBW (kg) | (33.85–44.65), 39.15 * | (34.30–46.40), 41.00 * | 0.49 |
| TBW (%) | 51.00 (±5.10) | 50.06 (±6.81) | 0.46 |
| ECW (kg) | (15.15–19.45), 17.20 * | (15.40–19.55), 18.15 * | 0.52 |
| ICW (kg) | (19.05–25.50), 22.00 * | (19.30–27.30), 22.45 * | 0.44 |
| ECW/TBW × 100% | 43.58 (±2.67) | 43.25 (±3.65) | 0.62 |
| Metabolic age | 53.81 (±15.24) | 45.68 (±15.48) | 0.02 |
| BMR (kcal) | (1279.00–1701.00), 1493.00 * | (1395.50–1888.50), 1561.50 * | 0.08 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). FFM—fat-free body mass; TBW—total body water; ECW—extracellular water; ICW—intracellular water; ECW/TBW%—ratio of extracellular water to total body water; BMR—basal metabolic rate.

### 3.6. Multivariate Analysis

To reduce the bias with age between the long COVID group and the non-long COVID population, one-to-one nearest-neighbor propensity score matching was used. The propensity score estimation was conducted using logistic regression. Next, the patients were matched according to age to verify whether the observed differences between long COVID and non-long COVID groups before matching for the following age-dependent parameters, i.e., A, $HR_{max}$, $VO_{2max}$, FEV1, FVC, FEV1/FVC [%], as well as RER and GFR, will present similar associations after age correction. The difference in age in long COVID and non-long COVID groups before and after matching is presented in Figure 2.

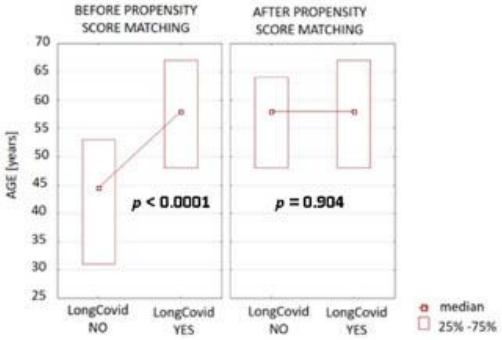


**Figure 2.** The differences in age between the long COVID and non-long COVID populations before and after matching.

The analysis indicated that the long COVID and non-long COVID age-matched populations did not differ in the following parameters: $HR_{max}$, $VO_{2max}$, and RER. However, the remaining analyzed parameters differ significantly between the analyzed groups (Table 6).

**Table 6.** Significant differences among the investigated groups after propensity score matching.

| Parameter | Patients with Symptoms n = 44 | Patients without Symptoms n = 102 | *p* |
|---|---|---|---|
| A (cm/s) | (60.00–83.00), 69.00 * | (58–78), 67 * | 0.04 |
| FVC (L) | (3.08–4.27), 3.53 * | (3.80–4.30), 4.26 * | 0.0001 |
| FEV1 (L) | (2.55–3.54), 2.90 * | (2.91–3.53), 3.11 * | 0.045 |
| FEV1/FVC (%) | (99.00–112.00), 106.50 * | (95.00–102.00), 96.00 * | <0.0001 |
| GFR (mL/min/1.73 $m^2$) | (76.10–98.80), 88.25 * | (79.88–109.80), 93.20 * | 0.04 |

*—median; values with a non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as the mean ± standard deviation (SD). A—late diastolic filling velocity; FVC—forced vital capacity; FEV1—forced expiratory volume in one second; FEV1/FVC—ratio of forced expiratory volume in one second to forced vital capacity; GFR—glomerular filtration rate.

Parameters with a *p*-value < 0.05 in the univariate analysis were entered into the multivariate analysis using the logistic regression analysis. This analysis pointed out that FEV1/FVC [%] higher than 102 is associated with a high chance of the occurrence of long-term symptoms after SARS-CoV-2 infection (OR = 6.27, 95% CI: 2.64–14.86; $p < 0.001$). Results are presented in Table 7.

**Table 7.** Multivariate analysis—stepwise logistic regression.

| Variable | OR | 95% CI for OR | | *p* |
|---|---|---|---|---|
| | | Lower Limit | Upper Limit | |
| FEV1/FVC% > 102% | 6.27 | 2.64 | 14.86 | <0.001 |

FEV1/FVC—ratio of forced expiratory volume in one second to forced vital capacity.

## 4. Discussion

As far as we can tell, the presented study is one of the first analyses of the relationship between echocardiographic, spiroergometric parameters, and hydration status in patients with long COVID symptoms. Patients with long COVID symptoms presented with significantly higher age, metabolic age, LA diameter, LVMI, A velocity, E/E', and lower E/A compared to the control group. Several teams of researchers have investigated the long-term effects of COVID-19 [11].

Tudoran et al. enrolled 150 patients with no cardiovascular disease, treated them as COVID-19 patients for 4 to 12 weeks before the inclusion of this study and assessed the cardiovascular condition using TTE. The 38 patients (approximately 25%) have found signs of heart disease, including pulmonary hypertension (9%), decreased left ventricular function (8%), diastolic dysfunction (14%), and/or evidence of pericarditis (10%) [22]. In another study, after the diagnosis of COVID-19, the authors detected RV dilation, increased pulmonary pressure, and biventricular dysfunction [23]. Our findings also revealed that LA diameter and LVMI were higher in the study group than in the control group. LA dilation is part of the heart remodeling process in various cardiovascular diseases and is associated with a worse outcome [24]. This abnormality may lead to blood stasis and the formation of thrombi. Furthermore, LA enlargement can indicate other risk factors for strokes and deaths, such as atrial fibrillation, structural heart disease, hypertension, or increased left ventricular mass [11,25]. Our next results show that long COVID patients presented with lower FVC, FEV1, $VO_{2max}$, RER, and higher FEV1/FVC% in comparison to healthy controls. There are a number of studies investigating changes in pulmonary function in patients post-COVID-19. Fumagalli et al. assessed respiratory function at the time of clinical recovery, 6 weeks, 6 months, and 12 months after discharge in patients surviving COVID-19 pneumonia. They revealed that COVID-19 pneumonia may result in significant alterations

in lung function, with a mainly restrictive pattern, partly persisting at 6 weeks after recovery from the acute phase but significantly improving during a 12-month follow-up period [26]. Some authors used CPET for the evaluation of long COVID symptoms. In the study by Mancini et al., 58.5% of patients 3 months after SARS-CoV-2 infection had decreased peak $VO_2$ in CPET [27]. Durstenfeld et al. conducted a meta-analysis to estimate the differences in exercise capacity among individuals with and without long COVID symptoms. Based on a meta-analysis of nine studies, including 464 symptomatic and 359 asymptomatic patients, the mean peak $VO_2$ was −4.9 (95% CI, −6.4 to −3.4) mL/kg/min [28]. The laboratory results in our study showed that patients with long COVID symptoms had lower rates of RBC and GFR and higher levels of glucose and hsTnT. The mentioned parameters are statistically significant, but in clinical practice, they may not be important. However, there are various studies concerning biochemical and hematological abnormalities in patients post-COVID-19. Kubankova et al. found significant phenotypic changes in the RBCs of recovered COVID-19 patients. RBCs are less deformable, smaller, and more heterogeneous in size and deformation [29]. Another study revealed that patients who survived COVID-19 were at greater risk of kidney dysfunction in the post-acute phase of the disease [30]. Some studies also demonstrated the risk of developing hyperglycemia and diabetes after SARS-CoV-2 infection [8,31]. Troponin T is a part of the troponin complex, which is composed of proteins integral to the contraction of skeletal and heart muscles. Cardiac troponin T (cTnT) is the preferred biochemical marker for myocardial cell necrosis [32]. Measurement of the hs-cTnT may provide strong prognostic information in patients with acute coronary syndromes, stable coronary artery disease, heart failure, and even in the general population. Several studies detected higher levels of hsTnT in COVID-19 patients. In one meta-analysis, the authors showed that elevated troponin was associated with mortality rates in patients with COVID-19, with 55% sensitivity and 80% specificity [33]. The results of several logistic regression models independently associated with the long-term symptoms of COVID were FEV1/FVC%. In a study conducted by Daitch et al., 2333 participants who recovered from COVID-19 were evaluated over an average of five months [146 days (95% CI 142–150)] after the initial COVID-19. The average age was 51 years, and 20% were over 65 years. Older adults are more likely to develop symptoms, and the most common symptoms are fatigue (38%), followed by diarrhea (30%). They complained of coughing and arthritis and were more likely to undergo abnormal chest imaging and lung function tests [34].

Long COVID can significantly impact a person's quality of life, and its management often requires a multidisciplinary approach involving healthcare professionals from various specialties. Research is ongoing to better understand the condition, develop effective treatments, and support individuals affected by long COVID. In one study, the authors examined the heterogeneity of adoption and use of U09.9, the ICD-10-CM code for "Post COVID-19 condition, unspecified." The research identifies common co-occurring diagnoses, categorizing them into cardiopulmonary, neurological, gastrointestinal, and comorbid conditions. It also reveals a demographic skew, with a higher representation of female, White, non-Hispanic individuals residing in areas with low poverty and unemployment rates among patients diagnosed with long COVID [35]. Izzo et al. highlighted the role of microRNA in cardiovascular complications associated with COVID-19, examining their potential utility as biomarkers, prognostic indicators, and targets for therapeutic interventions [36].

According to the results of the studies mentioned above, it is important to emphasize the role of vaccination against SARS-CoV-2. Vaccines help prevent severe illness, hospitalization, and death caused by COVID-19 [37]. They also contribute to reducing the transmission of the virus within communities. By achieving widespread vaccination coverage, we can establish herd immunity, protecting vulnerable populations and allowing societies to safely return to normalcy [38].

The presented study has potential limitations, including a small study population (146 participants). This study design was limited regarding the evaluation of the effects of used medications. In addition, only patients who were able to perform CPET were enrolled. We were also unable to measure total lung capacity (TLC) and diffusion lung

capacity for carbon monoxide (DLCO). Furthermore, we assessed TTE only at rest. Some echocardiographic parameters, such as left atrial strain, were not obtained. These data need to be interpreted with caution. Therefore, future studies, including the measurement of TLC and DLCO in a larger post-COVID population, are recommended.

The strengths of our study are that this is one of the first studies to evaluate the utility of selected echocardiographic, laboratory, and spiroergometric parameters in differentially diagnosing patients presenting the symptoms of long COVID.

## 5. Conclusions

In conclusion, an FEV1/FVC% higher than 102 is associated with a high chance of the occurrence of long-term symptoms after SARS-CoV-2 infection. Persistent symptoms of long COVID can mimic those of cardiovascular disease.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in this study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Data Availability Statement:** Individual participant data that underlie the results reported in this article after deidentification (text, tables, figures, and appendices) as well as the study protocol will be available for researchers who provide a methodologically sound proposal. Proposals may be submitted after 9 months and up to 36 months following article publication.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# Predictors of Long-COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery

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**Abstract:** Background: The aim of the study was to identify factors that may cause the presence of long COVID and to assess factors that affect chronic limited exercise tolerance in spiroergometry after one-year follow-up in patients who had recovered from COVID-19. Methods: Of 146 patients hospitalised in the Cardiology Department, 82 completed a one-year follow-up (at least 15 months post-COVID-19 recovery). We compared their conditions at initial screening and follow-up to analyse the course of long COVID and exercise intolerance mechanisms. Clinical examinations, laboratory tests, echocardiography, cardiopulmonary exercise testing, and body composition analysis were performed. Results: The patients, after one-year follow-up, had significantly higher levels of high-sensitivity cardiac troponin T (hs-cTnT) ($p = 0.03$), left atrium diameter (LA) ($p = 0.03$), respiratory exchange ratio (RER) ($p = 0.008$), and total body water content percentage (TBW%) ($p < 0.0001$) compared to the 3-month assessment. They also had lower forced vital capacity in litres (FVC) ($p = 0.02$) and percentage (FVC%) ($p = 0.001$). The factors independently associated with a decline in maximum oxygen uptake ($VO_{2max}$) after one-year follow-up included the percentage of fat (OR 2.16, 95% CI: 0.51–0.77; $p = 0.03$), end-diastolic volume (EDV) (OR 2.38, 95% CI 0.53–0.78; $p = 0.02$), and end-systolic volume (ESV) (OR 2.3, 95% CI: 0.52–0.78; $p = 0.02$). Conclusions: Higher left ventricular volumes and fat content (%) were associated with a reduced peak $VO_{2max}$ when assessed 15 months after COVID-19 recovery.

**Keywords:** COVID-19; long COVID; spiroergometry; maximal oxygen uptake; body mass analysis

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## 1. Introduction

COVID-19 is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak began as an epidemic on 17 November 2019, in Wuhan, located in central China, and was officially classified as a pandemic by the World Health Organisation (WHO) on 11 March 2020. The COVID-19 pandemic caused an unprecedented disturbance in healthcare worldwide [1–3]. Although many individuals recover fully from COVID-19, a significant number continue to experience persistent symptoms and functional limitations, even after a year or more from the initial diagnosis [4,5]. One of the most common symptoms reported in these individuals is exercise intolerance, which can greatly impact their quality of life. Understanding the predictors of chronic impairment of exercise tolerance in patients after COVID-19 is crucial for better management and rehabilitation strategies [6]. Furthermore, it should be noted that the long-term effects of COVID-19 are still actively being researched. New information about the virus and its impact on different body systems continues to emerge. Therefore, the list of predictors can

evolve as researchers gain a deeper understanding of the long-term consequences of the disease. Assessing exercise tolerance using spiroergometry can provide valuable insight into the functional capacity of individuals after COVID-19 [7]. It allows the measurement of oxygen consumption, carbon dioxide production, and other respiratory parameters during exercise [8]. By identifying the predictors of chronic impairment of exercise tolerance, healthcare professionals can develop customised rehabilitation programmes that address specific limitations and improve overall fitness and well-being in patients after COVID-19. It is important to emphasise the multidisciplinary approach to the management of patients post-COVID-19, including respiratory physicians, cardiologists, physiotherapists, and other relevant specialists [9]. Comprehensive evaluations, including spiroergometry, along with clinical evaluations and medical imaging, can help identify predictors and guide the development of appropriate treatment strategies to optimise recovery and enhance exercise tolerance in patients after COVID-19 [10]. This study aimed to investigate the underlying mechanisms of these symptoms in patients with long-COVID. The purpose of the study was to compare and identify factors that contribute to chronic limited exercise tolerance in patients after one year of follow-up after COVID-19.

## 2. Materials and Methods

### 2.1. Basic Characteristics

Out of the 146 consecutive patients (38% males, 62% females) who had been hospitalised in the Department of Cardiology and had recovered from COVID-19 3 to 6 months after confirmed diagnosis, 82 (56%) (35 males, 47 females) completed a 1-year follow-up, which occurred at least 15 months after the initial COVID-19 diagnosis. Patients were assigned to appropriate groups based on the WHO definition of long COVID. The long COVID patients presented with the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation [11]. We compared the same patients' condition after 3–6 months and after 1-year follow-up from recovery to establish the course of long-COVID and the mechanism of chronic exercise intolerance after COVID-19. The average age of patients at inclusion was 54. Every participant included in the study conducted a cardiopulmonary exercise testing (CPET) on the ergometer. The patients did not participate in rehabilitation programs and did not increase their daily physical activities during the interval between assessments. The patients in the study groups maintained a sedentary lifestyle. The study was approved by the Polish Mother's Memorial Hospital Research Institute (PMMHRI-BCO.75/2020) and is in compliance with the Declaration of Helsinki [7].

Exclusion criteria:

- Heart failure diagnosis or typical symptomatic heart failure;
- Previous myocardial infarction;
- Uncontrolled arterial hypertension;
- Unstable angina;
- Acute pericarditis or myocarditis;
- Active endocarditis;
- Acute pulmonary embolism;
- History of stroke, transient ischemic attack, or intracerebral haemorrhage;
- Unstable heart rhythm disorders;
- Advanced atrioventricular block;
- Cardiomyopathy diagnosis (dilated, hypertrophic, postpartum, restrictive, tachyarrhythmic);
- Active systemic infection;
- Carrier of Hepatitis B virus (HBV), Hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or testing positive for hepatitis B surface antigen (HBsAg) or antibodies to HCV;
- Drug and alcohol abuse;
- Chronic kidney disease (stage IV and V according to the National Kidney Foundation) and dialysis treatment;

- Severe hypothyroidism and hyperthyroidism;
- Active autoimmune disease;
- Use of cytostatic drugs, immunosuppressants, glucocorticosteroids, or antiretroviral drugs;
- Documented neoplastic process;
- History of bone marrow transplantation or other organ transplantation, as well as treatment with blood products within the last 6 months;
- Underwent surgery or a significant injury in the last month;
- Pregnancy or lactation;
- A physical limitation that hinders the completion of a spiroergometric test;
- Patient's incapacity to cooperate and/or provide informed consent to participate in research;
- Individuals who did not provide their informed consent to take part in the study [7].

### 2.2. Echocardiography

Echocardiograms were conducted using the Vivid E95 system (GE Healthcare, Chicago, IL, USA) [7]. Measurements were performed according to current guidelines [12]. To determine the volume and ejection fraction (EF) of the left ventricular (LV), the modified Simpson's rule was employed. The estimation of the left atrial (LA) volume utilised the modified biplane Simpson's method, employing apical 2- and 4-chamber views at end-systole. The resulting volume was indexed to the patient's body surface area to derive the LA volume index (LAVi) [13]. Various other measurements were analysed, including maximal early (E) and late (A) transmitral velocities, as well as the ratio of early to late diastolic transmitral flow velocity (E/A) [14]. Global peak systolic strain (GLPS) assessment was conducted via speckle tracking echocardiography [15]. Evaluation of right ventricular (RV) function involved obtaining measurements such as tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler echocardiography (TDE) [16].

### 2.3. Spiroergometry

Cardiopulmonary exercise testing (CPET) was performed using an upright cycle ergometer called Bike M, which features electromagnetic braking (CORTEX Biophysik GmbH, Leipzig, Germany) [7]. Metabolic gas analysis was performed using the METALYZER 3B system (CORTEX Biophysik GmbH, Leipzig, Germany) with the assistance of the MetaSoft Studio application software (version 5.8.3) developed by CORTEX systems [17]. Before each test, the system underwent calibration using a standard gas mixture of known concentrations. The breath gas analyser was internally calibrated just before each measurement. Both the volume of gases and the flow sensor were calibrated immediately before the test, with their calibration validated twice yearly. Following a 5-min rest on the cycle ergometer, exercise began at 50 W, and, subsequently, the workload was raised by 25 W every 3 min. Before exercise testing on the bicycle ergometer, spirometry was conducted to assess lung function. Forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC) were assessed. The $FEV_1$/FVC ratio, also known as the Tiffeneau index, was recorded [18]. During CPET on the bicycle ergometer, the continuous monitoring of the non-invasive blood pressure (NIBP) using a sphygmomanometer Exacta (Rudolf Riester GmbH, Jungingen, Germany), heart rate (HR), 12-lead electrocardiogram (ECG) using an exercise electrocardiogram Meta control 3000 (CORTEX Biophysik GmbH, Leipzig, Germany), and oxygen saturation ($SpO_2$) were carried out. One of the key measurements obtained during CPET is maximum oxygen uptake ($VO_{2max}$), which represents the highest level of oxidative metabolism achievable by engaging large muscle groups. If a clear plateau is not observed in the oxygen uptake curve, the highest $VO_2$ achieved, referred to as $VO_2$ peak, can be used as a substitute for $VO_{2max}$ [19]. Furthermore, several other valuable CPET parameters were evaluated. These derived measurements include ventilatory exchange (VE), oxygen uptake ($VO_2$), carbon dioxide expenditure ($VCO_2$), respiratory exchange ratio (RER), anaerobic threshold (AT), oxygen uptake at the anaerobic threshold ($VO_2AT$), and the slope of minute ventilation to carbon dioxide production ($VE/VCO_2$ slope) [20].

### 2.4. Body Mass Analysis

The Segmental Body Composition Analyser (Tanita Pro, Tokyo, Japan) is a non-invasive tool used for analysing body mass [7]. This device utilises various methods, such as Dual-energy X-ray absorptiometry (DXA) and the dilution method, for total body water measurement employing the Bioelectrical Impedance Analysis (BIA) method [21]. The analyser then proceeded to provide separate mass readings for different body segments and estimated values for total, regional fat mass (FM), and fat-free mass (FFM). Furthermore, measurements were taken for total body water (TBW), intracellular water (ICW), and extracellular water (ECW). The correlation involving ECW/TBW, defined as the ECW/TBW percentage ratio, and basal metabolic rate (BMR) were also examined [22].

### 2.5. Statistical Analysis

Analysis was performed using the STATISTICA 13.1 software package (StatSoft, Krakow, Poland). Normal distribution was assessed using the Shapiro–Wilk test. The Wilcoxon signed-rank test was applied for variables. Significant continuous data from univariate analyses were used to create receiver-operating characteristic (ROC) curves, and the Youden index was utilised to convert these into categorical data. Backward stepwise multivariate logistic regression tested these categorical data. Results were deemed significant at a threshold of $p < 0.05$.

## 3. Results

### 3.1. Evaluation of Basic Characteristics

We compared 82 consecutive patients, who were hospitalised in the Department of Cardiology and had recovered from COVID-19 three to six months after confirmed diagnosis, examining the same patients during a one-year follow-up. There were no differences in medical treatment between the groups. The data are presented in Table 1.

**Table 1.** Evaluation of basic characteristics.

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| Clinical characteristics | | | |
| BMI (kg/m$^2$) | (23.24–30.42), 26.79 * | (24.03–30.25), 26.28 * | 0.32 |
| BSA (m$^2$) | (1.75–2.03), 1.86 * | (1.76–2.05), 1.88 * | 0.23 |
| SBP (mmHg) | (125.00–140.00), 130.00 * | (125.00–145.00), 132.00 * | 0.10 |
| DBP (mmHg) | (71.00–86.00), 80.00 * | (75.00–90.00), 82.00 * | 0.052 |
| Hypertension | 57% | 61% | 0.63 |
| Diabetes mellitus | 20% | 21% | 0.85 |
| Dyslipidaemia | 54% | 57% | 0.69 |
| Obesity | 24% | 29% | 0.48 |
| Alcohol | 4% | 2% | 0.68 |
| Smoking | 11% | 16% | 0.36 |

*—median; values with non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). BMI—body mass index; BSA—body surface area; SBP—systolic blood pressure; DBP—diastolic blood pressure.

### 3.2. Evaluation of Laboratory Tests

Follow-up subjects presented a significantly higher level of hs-cTnT (median 5.8 (IQR: 3.9–9.3) vs. 4.9 (IQR: 3.2–8.4) pg/mL, $p = 0.03$). There were no statistically significant differences in residual laboratory parameters. The data are shown in Table 2.

**Table 2.** Evaluation of laboratory tests among investigated groups.

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| Laboratory tests | | | |
| hs-cTnT (pg/mL) (<14.00) | (3.20–8.40), 4.90 * | (3.90–9.30), 5.80 * | 0.03 |
| NT-proBNP (pg/mL) (<125.00) | (42.00–125.00), 87.00 * | (51.00–120.00), 82.00 * | 0.80 |
| RBC ($10^6$/µL) (women—3.80–5.80, men—4.50–6.50) | (4.20–4.90), 4.50 * | (4.20–4.90), 4.50 * | 0.37 |
| Haemoglobin (g/dL) (women—12.00–15.00; men—13.00–18.00) | (12.80–14.60), 13.70 * | (12.60–14.80), 13.40 * | 0.32 |
| PLT ($10^3$/µL) (150.00–400.00) | (165.00–224.00), 205.00 * | (172.00–238.00), 210.00 * | 0.70 |
| Creatinine (mg/dL) (0.55–1.02) | (0.67–0.91), 0.79 * | (0.65–0.93), 0.77 * | 0.97 |
| GFR (ml/min/1.73 $m^2$) (>90.00) | (79.10–104.10), 92.20 * | (79.60–103.80), 91.50 * | 0.26 |
| Urea (mg/dL) (17.00–43.00) | (27.00–40.00), 32.00 * | (27.00–38.00), 41.00 * | 0.59 |
| Glucose (mg/dL) (60.00–99.00) | (85.00–96.00), 90.00 * | (84.00–96.00), 91.00 * | 0.66 |
| HDL cholesterol (mg/dL) (>40.00) | (39.00–59.00), 49.50 * | (40.00–57.00), 47.50 * | 0.58 |
| LDL cholesterol (mg/dL) (<115.00) | (70.00–110.00), 94.00 * | (62.00–106.00), 85.00 * | 0.27 |
| Triglycerides (mg/dL) (<150.00) | (83.00–148.00), 103.50 * | (78.00–130.00), 100.00 * | 0.07 |
| Total cholesterol (mg/dL) (<200.00) | (135.00–188.00), 169.00 * | (130.00–188.00), 161.00 * | 0.33 |
| ALT (U/L) (<50.00) | (17.00–29.00), 22.00 * | (17.00–30.00), 22.00 * | 0.59 |
| AST (U/L) (<50.00) | (25.00–31.00), 27.00 * | (25.00–32.00), 28.00 * | 0.73 |
| CRP (mg/dL) (<0.50) | (0.50–0.50), 0.50 * | (0.50–0.50), 0.50 * | 0.22 |
| D-dimer (ng/mL) (<500.00) | (200.50–398.50), 286.00 * | (167.00–326.00), 224.00 * | 0.19 |
| K (mmol/L) (3.50–5.10) | (4.20–4.60), 4.40 * | (4.20–4.60), 4.40 * | 0.78 |
| Na (mmol/L) (135.00–145.00) | (138.00–141.00), 139.00 * | (138.00–141.00), 140.00 * | 0.29 |

*—median; values with non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). Hs-cTnT—high-sensitivity cardiac troponin; NT-proBNP—N-terminal prohormone of brain natriuretic peptide; RBC—red blood cells; PLT—thrombocytes; GFR—glomerular filtration rate; HDL—high-density lipoprotein; LDL—low-density lipoprotein; ALT—alanine aminotransferase; AST—aspartate aminotransferase; CRP—c-reactive protein; K—serum potassium; Na—serum sodium.

### 3.3. Evaluation of Echocardiography

The LA diameter was significantly higher in patients in one year follow-up [median 38 (IQR: 34–43) vs. 36 (IQR: 34–43) mm, $p = 0.03$]. The results are presented in Table 3.

**Table 3.** Evaluation of selected echocardiographic parameters among investigated groups.

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| Echocardiography | | | |
| EF (%) | (55.00–65.00), 62.00 * | (58.00–65.00), 63.00 * | 0.27 |
| EDV ($cm^3$) | (75.00–105.00), 92.00 * | (77.00–117.00), 99.00 * | 0.055 |
| ESV ($cm^3$) | (26.00–48.00), 37.00 * | (28.00–48.00), 37.00 * | 0.26 |
| LA (mm) | (34.00–43.00), 36.00 * | (34.00–43.00), 38.00 * | 0.03 |
| LAVi ($ml/m^2$) | (26.00–41.00), 34.00 * | (27.00–42.00), 33.00 * | 0.45 |
| E (cm/s) | (62.00–87.00), 75.00 * | (63.00–96.00), 78.00 * | 0.43 |
| A (cm/s) | (54.00–80.00), 67.00 * | (54.00–75.00), 65.00 * | 0.85 |
| E/A | (0.87–1.44), 1.12 * | (0.92–1.49), 1.14 * | 0.25 |
| GLPS (%) | (18.80–20.80), 20.00 * | (18.10–20.10), 19.10 * | 0.94 |
| TAPSE (mm) | (20.00–26.00), 23.00 * | (20.00–25.00), 22.00 * | 0.63 |
| TDE S' (cm/s) | (12.00–15.00), 13.00 * | (11.00–15.00), 13.00 * | 0.06 |

*—median; values with non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). EF—left ventricular ejection fraction; EDV—end-diastolic volume; ESV—end-systolic volume; LA—left atrium; LAVi—left atrial volume index; E—early diastolic filling velocity, A—late diastolic filling velocity; E/A—ratio of early to late diastolic transmitral flow velocity; GLPS—global peak systolic strain; TAPSE—tricuspid annular plane systolic excursion; TDE S'—tissue Doppler echocardiography.

### 3.4. Evaluation of Spiroergometry

During follow-up, the subjects presented with higher RER (median 1.10 (IQR: 1.05–1.13) vs. 1.09 (IQR: 1.02–1.12), $p = 0.008$) and lower FVC (L), FVC (%) (median 3.71 (IQR: 2.88–4.27) vs. 3.79 (IQR: 3.18–4.44) L, $p = 0.02$; median 101 (IQR: 91–112) vs. 105 (IQR: 95–117) %, $p = 0.001$; respectively). There were no significant differences with respect to the other parameters. The data are demonstrated in Table 4.

**Table 4.** Evaluation of spiroergometry among investigated groups.

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| Spiroergometry | | | |
| Exercise time (s) | (402.00–696.00), 518.00 * | (420.00–756.00), 609.00 * | 0.30 |
| HR max | (122.00–164.00), 146.00 * | (124.00–166.00), 142.00 * | 0.59 |
| Peripheral SBP max (mmHg) | (140.00–200.00), 160.00 * | (150.00–190.00), 165.00 * | 0.63 |
| Peripheral DBP max (mmHg) | (70.00–90.00), 80 * | (80.00–90.00), 80.00 * | 0.02 |
| $FEV_1$ (l) | (2.55–3.56), 2.99 * | (2.45–3.53), 3.04 * | 0.07 |
| FVC (l) | (3.18–4.44), 3.79 * | (2.88–4.27), 3.71 * | 0.02 |
| FVC% | (95.00–117.00), 105.00 * | (91.00–112.00), 101.00 * | 0.001 |

Table 4. *Cont.*

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| $FEV_1/FVC$ | (76.00–85.00), 82.00 * | (77.00–88.00), 82.00 * | 0.16 |
| $FEV_1/FVC\%$ | (96.00–109.00), 103.00 * | (97.00–111.00), 103.00 * | 0.16 |
| FEF 25–75 (l/s) | (1.88–3.35), 2.72 * | (2.04–3.74), 3.02 * | 0.34 |
| RER | (1.02–1.12), 1.09 * | (1.05–1.13), 1.10 * | 0.008 |
| $VO_{2max}$ (ml/min/kg) | (17.00–26.00), 21.00 * | (18.00–26.00), 22.00 * | 0.12 |
| $VO_{2max\ pred}$ (%) | (71.00–104.00), 81.00 * | (71.00–98.00), 85.00 * | 0.53 |
| $VO_2AT$ (ml/min/kg) | (11.00–18.00), 14.00 * | (11.00–16.00), 13.00 * | 0.38 |
| Peak $VO_{2max}$ (l) | (1.25–1.98), 1.65 * | (1.32–1.98), 1.63 * | 0.56 |
| $VE/VCO_2$ slope | (25.60–32.70), 29.60 * | (26.50–33.30), 29.10 * | 0.67 |

*—median; values with non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). DBP—diastolic blood pressure; SBP—systolic blood pressure; $FEV_1$—forced expiratory volume in one second; FVC—forced vital capacity; $FEV_1/FVC$—ratio of forced expiratory volume in one second to forced vital capacity; FEF 25–75%—forced expiratory flow over the middle one half of the FVC; RER—respiratory exchange ratio; $VO_{2max}$—the maximum amount of oxygen the body can utilise during a specified period of usually intense exercise; $VO_{2max\ pred}$—predicted value of $VO_{2max}$; $VO_2AT$—oxygen uptake at anaerobic threshold per kilogram; peak $VO_2$—highest respiratory oxygen uptake ($VO_2$) achieved by the subject during the maximal exercise; $VE/VCO_2$ slope—the minute ventilation/carbon dioxide production slope.

### 3.5. Evaluation of Body Mass Analysis

Only TBW content in % was statistically significantly elevated in follow-up patients (median 53.1 (IQR: 49.3–57.9) vs. 49.5 (IQR: 47.8–56.0)%, $p < 0.0001$). The results are shown in Table 5.

Table 5. Evaluation of body mass analysis among investigated groups.

| Parameter | Patients Hospitalised Three to Six Months after COVID-19 Diagnosis $n = 82$ | Patients Hospitalised in One-Year Follow-Up $n = 82$ | $p$ |
|---|---|---|---|
| Body mass analysis | | | |
| Fat (%) | (22.30–34.10), 29.20 * | (23.80–33.40), 27.90 * | 0.96 |
| Fat (kg) | (16.00–29.20), 23.60 * | (17.70–28.90), 21.60 * | 0.45 |
| FFM (kg) | (48.00–62.50), 55.50 * | (48.80–64.50), 55.70 * | 0.67 |
| TBW (kg) | (34.30–44.70), 39.50 * | (35.10–48.10), 41.80 * | 0.07 |
| TBW (%) | (47.80–56.00), 49.50 * | (49.30–57.90), 53.10 * | <0.0001 |
| ECW (kg) | (15.30–19.60), 17.20 * | (15.20–20.90), 17.70 * | 0.06 |
| ICW (kg) | (19.40–25.50), 22.40 * | (20.50–27.30), 24.10 * | 0.17 |
| ECW/TBW × 100% | (40.80–45.30), 43.30 * | (40.70–45.50), 43.40 * | 0.93 |

*—median; values with non-normal distribution are expressed as median (range) values. Values with normal distributions are expressed as mean ± standard deviation (SD). FFM—fat-free body mass; TBW—total body water; ECW—extracellular water; ICW—intracellular water, ECW/TBW%—ratio of extracellular water to total body water.

### 3.6. Multivariate Analysis

In a multiple logistic regression model, the two factors were found to be significantly associated with a worsening of $VO_{2max}$ in the follow-up: percentage of fat (OR 2.16, 95% CI: 0.51–0.77; $p = 0.03$), end-diastolic volume (EDV) (OR 2.38, 95% CI 0.53–0.78; $p = 0.02$), and

end-systolic volume (ESV) (OR 2.3, 95% CI: 0.52–0.78; $p = 0.02$). The results are presented in Table 6 and Figure 1.

**Table 6.** Multivariate analysis.

| Variable | OR | 95% CI for OR | | *p* |
|---|---|---|---|---|
| | | Lower Limit | Upper Limit | |
| Fat (%) | 2.16 | 0.51 | 0.77 | 0.03 |
| EDV ($cm^3$) | 2.38 | 0.53 | 0.78 | 0.02 |
| ESV ($cm^3$) | 2.30 | 0.52 | 0.78 | 0.02 |

EDV—end-diastolic volume; ESV—end-systolic volume.

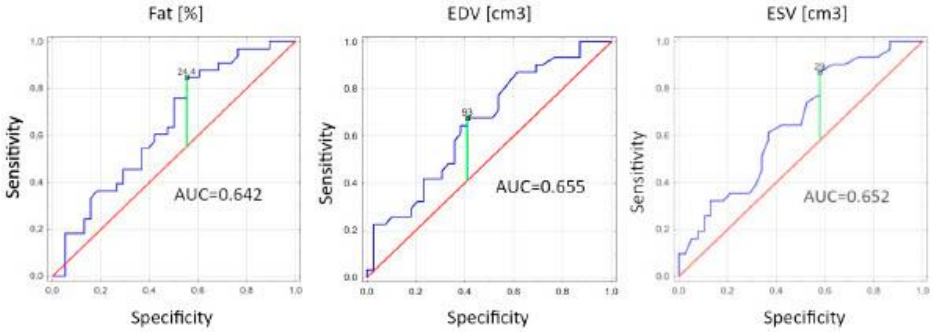


**Figure 1.** Receiver-operating curve (ROC) for the fat (%), end-diastolic volume (EDV) and end-systolic volume (ESV) variables revealing their diagnostic potential. AUC—area under the ROC curve; blue line—graphical plot of studied parameter determining the area under the curve, green line—the line pointed at Youden point, red line—reference line.

## 4. Discussion

The findings of this study suggest that several factors contribute to the chronic impairment of exercise tolerance in patients after COVID-19. At one year of follow-up, pateints presented elevated levels of hs-cTnT. In a prior study, where we compared patients three to six months after their COVID-19 diagnosis, subjects with symptoms also exhibited higher levels of hs-cTnT [7]. It is important to underscore that hs-cTnT remained within the boundaries of the normal range in both groups under comparison. The findings emphasise that the differences observed between these two groups do not signify an acute cardiac issue or significant myocardial damage, at least as assessed by hs-cTnT levels. Hs-cTnT is a specific biomarker used in the diagnosis and evaluation of heart-related conditions [23]. The Hs-cTnT test utilises advanced techniques that can detect lower levels of troponin T in the blood with increased sensitivity and precision [24]. This allows the early detection of myocardial injury and a more accurate assessment of cardiac conditions. The test measures the concentration of hs-cTnT in the blood and compares it with established reference ranges to aid in the diagnosis and stratification of patients with suspected heart-related problems. The clinical significance of troponin elevation, even when still within the normal range, and its impact on cardiovascular outcomes are still uncertain. In contrast to our results, there are few studies on persistently elevated troponin levels in post-COVID-19 patients. In a study by Kotecha et al., cardiac magnetic resonance imaging (CMR) revealed late gadolinium and/or ischaemia in 54% of patients with severe COVID-19 and persistent elevation of troponin elevation at around 68 days after discharge [25]. Similar CMR findings have been observed in patients with mild COVID-19 six months after infection compared to healthy

individuals, as demonstrated by Joy et al. [26]. However, the long-term implications of these findings and their clinical relevance are yet to be determined.

Our next findings indicated that follow-up subjects had a higher RER. Furthermore, in the aforementioned previous research study, patients without symptoms three to six months after a COVID-19 diagnosis also exhibited higher RER [7]. The RER is a physiological parameter that indicates the ratio between carbon dioxide ($CO_2$) production and oxygen ($O_2$) consumption during cellular respiration. It is calculated by dividing the volume of carbon dioxide produced ($VCO_2$) by the volume of oxygen consumed ($VO_2$). The RER value provides insights into whether the body is primarily using carbohydrates (RER close to 1.0) or fats (RER close to 0.7) for energy [27,28]. An RER exceeding 1.0 indicates an increasing reliance on anaerobic metabolism, which often accompanies higher exercise intensity and a transition to less sustainable energy sources. Notably, an RER surpassing 1.10 is commonly used as a criterion for exhaustion [29]. In the study of Joris et al., CPET was performed in critically ill survivors [30]. Their metabolic efficiency was low at 15.2 (12.9–17.8)%. The 50% decrease in $VO_2$ after maximum effort was delayed, at 130 (120–170) s, with a RER that was still high (1.13 [1–1.2]). In the presented study, the higher median RER in the follow-up group (1.10) compared to the comparison group (1.09) suggests an increased reliance on carbohydrates as an energy source in the follow-up patients. The elevated RER in the follow-up group might suggest altered metabolic responses or increased reliance on anaerobic metabolism during exercise. The significance of these results could prompt further investigations into the underlying mechanisms contributing to the observed differences in RER.

Total body water (TBW) refers to the total amount of water present in a person's body. It represents the sum of water content in all body compartments, including intracellular and extracellular fluid [31]. TBW plays a vital role in various physiological processes, such as maintaining hydration, regulating body temperature, transporting nutrients, facilitating waste removal, and supporting cellular function. The exact TBW value can vary depending on factors such as age, sex, body composition, and overall health. On average, TBW accounts for about 50–70% of the total body weight in adults, with higher percentages typically seen in infants and children due to their higher water content relative to body weight [32]. The TBW content can be estimated using the BIA method. In our study, we demonstrated that the follow-up patients had higher TBW content. In our other study, we showed that hydration status is related to limited exercise tolerance after 3 to 6 months after the diagnosis of COVID-19 in patients with normal LVEF [6]. However, in the comparison of patients three to six months after their COVID-19 diagnosis, there were no statistically significant differences regarding hydration status [7]. Some studies investigated the association between body mass compartments and the severity of COVID-19. Cornejo-Pareja demonstrated that overhydration was an important predictor of COVID-19 mortality [33].

Forced vital capacity (FVC) is a commonly used measurement in pulmonary function testing to assess lung function. It is a measure of the maximum amount of air that a person can forcefully exhale after taking a deep breath. FVC is an essential parameter in the diagnosis and monitoring of various respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, and restrictive lung diseases [34]. It is important to note that FVC measurements are influenced by several factors, including age, sex, body position during testing, patient effort, and the presence of any respiratory muscle weakness or abnormalities of the respiratory muscles [35]. In this study, the follow-up subjects presented with decreased FVC. Furthermore, in the previously mentioned study, patients with symptoms presented a decreased FVC [7]. Some clinical observations have indicated that long-COVID can lead to persistent respiratory symptoms and abnormalities in lung function, including reduced FVC [36–38].

Our findings revealed that left ventricular volumes and fat content are associated with a reduced $VO_{2max}$ 15 months after COVID-19 recovery. In our previous study, there was no statistical significance regarding these parameters [7]. Brown et al. conducted a study on exercise, examining discharged patients with COVID-19 who self-reported reduced

exercise capacity. They compared them to discharged patients with normal exercise capacity, as well as a control group [39]. When adjusted for body surface area, the individuals with a history of COVID-19 exhibited a decrease in left ventricular end-systolic volume indexed to body surface area and an increase in left ventricular ejection fraction. Furthermore, those with reduced exercise capacity showed reduced index oxygen consumption, indexed stroke volume, and indexed left ventricular end-diastolic volume. In another study, 346 people with prior COVID infection underwent a baseline examination after a minimum of 4 weeks from the initial diagnosis of COVID-19 between April 2020 and October 2021 and a follow-up examination after a minimum of 4 months from baseline. The authors showed that female sex and small LV volumes and masses were associated with symptomatic status at follow-up [40]. The fat content in the body, specifically in terms of body composition, plays a significant role in overall health. Excess body fat, particularly when it accumulates in excess, can have implications for various aspects of health [41]. Mondal et al. conducted a study in which they presented findings that increased body fat is associated with a decreased level of $VO_2$ peak [42]. However, in another study, the authors revealed that the main influence of body weight on $VO_{2max}$ is explained by FFM, and fat content does not have any effect on oxygen consumption [43].

Furthermore, it is noteworthy that the patients in this study led sedentary lifestyles and did not participate in rehabilitation programs. This sedentary lifestyle could have contributed to the observed physiological changes, as physical inactivity can lead to deconditioning and further exacerbate exercise intolerance in long COVID patients. Incorporating rehabilitation programs tailored to the specific challenges faced by long COVID patients may play a significant role in improving their exercise tolerance and overall health.

## 5. Limitations

The presented study has certain limitations that should be taken into consideration. First, the study population consisted of a relatively small sample size, with only 82 participants. Additionally, the study design did not thoroughly evaluate the potential effects of the medications used by the participants. Furthermore, the study involved only patients capable of performing CPET. There were also limitations in terms of the measurements conducted. Diffusion lung capacity for carbon monoxide (DLCO) and total lung capacity (TLC) were not measured, which could provide valuable insights into lung function and gas exchange. Additionally, TTE was performed only at rest, and certain echocardiographic parameters, such as left atrial strain, were not obtained. Given these limitations, caution should be exercised when interpreting the data from this study. It is recommended that future studies address these limitations by including larger post-COVID populations and incorporating measurements of TLC and DLCO. Furthermore, conducting TTE assessments during exercise would further enhance our understanding of cardiac implications in post-COVID patients.

The strengths of our study lie in its pioneering approach as one of the first investigations to explore the potential of selected echocardiographic, laboratory, and spiroergometric parameters in the evaluation of patients after COVID-19 during a one-year follow-up.

## 6. Conclusions

In conclusion, after a 15 months period after COVID-19 recovery, patients showed elevated levels of hs-cTnT, RER, TBW%, and reduced FVC. Higher left ventricular volumes and fat content (%) were associated with a reduced peak $VO_{2max}$ assessed 15 months after COVID-19 recovery. These findings shed light on the factors that contribute to chronic exercise intolerance in patients after COVID-19 and emphasise the importance of the long-term monitoring and treatment of individuals affected by long COVID.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patient(s) to publish this paper.

**Data Availability Statement:** After deidentification, the individual participant data that underlie the results reported in this article (text, tables, figures and appendices), as well as study protocol, will be available for researchers who provide a methodologically sound proposal. Proposals may be submitted after 9 months and up to 36 months following article publication.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19

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**Abstract:** Coronavirus disease 2019 (COVID-19) is a severe respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Heart failure (HF) is associated with a worse prognosis for patients with this viral infection, highlighting the importance of early detection and effective treatment strategies. HF can also be a consequence of COVID-19-related myocardial damage. To optimise the treatment of these patients, one needs to understand the interactions between this disease and viruses. Until now, the validity of the screening for cardiovascular complications after COVID-19 has not been confirmed. There were also no patients in whom such diagnostics seemed appropriate. Until appropriate recommendations are made, diagnosis procedures must be individualised based on the course of the acute phase and clinical symptoms reported or submitted after COVID-19. Clinical phenomena are the criteria for determining the recommended test panel. We present a structured approach to COVID-19 patients with heart involvement.

**Keywords:** COVID-19; heart failure; inflammation; cardiopulmonary exercise testing; coagulopathy

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by coronavirus 2 of severe acute respiratory syndrome (SARS-CoV-2). It started as an epidemic on 17 November 2019 in Wuhan, Hubei Province, central China, and was declared a pandemic by the World Health Organisation (WHO) on 11 March 2020. At the end of 2022, more than 670 million cases of the SARS-CoV-2 virus has been registered in 192 countries and territories. There are nearly 20 million active cases, more than 640 million recoveries, and more than 6.60 million deaths. Typical symptoms of the disease include fever, dry cough, anosmia (loss of smell), ageusia (loss of taste), fatigue, and dyspnoea. Less common symptoms include sputum production, headache, chills, haemoptysis, chest pain, diarrhoea, nausea and vomiting, and a sore throat [1]. Most cases of the disease are mild, but some may lead to pneumonia or multiple organ failure. Some patients have only gastrointestinal symptoms. Developing a viral infection can lead to pneumonia, acute respiratory distress syndrome (ARDS), sepsis and septic shock, and death. It can also cause a number of cardiac complications, such as arrhythmias, cardiogenic shock, acute myocardial injury, and ST changes on the electrocardiogram (ECG) [2]. In a multicentre cohort study, the authors found a high incidence of heart failure (23%) as an extrapulmonary manifestation of infection, and the rate was higher (52%) in non-survivors [3]. It is still debatable whether this is due to viral myocardial disease or as a result of the cytokine storm and rapid inflammatory

response. The pathophysiology of SARS-CoV-2 is characterised by the overproduction of inflammatory cytokines leading to systemic inflammation and multiorgan dysfunction syndrome, which acutely affects the cardiovascular system.

The mechanisms of cardiovascular injury caused by SARS-CoV-2 infection are not fully understood, but the primary mechanism involves the virus infiltrating host cells via angiotensin converting enzyme 2 (ACE2). ACE2, a membrane protein, plays a vital role in mitigating the adverse effects of the renin–angiotensin–aldosterone system (RAAS) by converting angiotensin II (Ang II) to Ang- (1–7) [4]. ACE2 is predominantly present in the vascular endothelium of various tissue structures, including lung cells, smooth muscle cells within the pulmonary vascular system, bronchial epithelium, epithelial cells in the lungs, heart, blood vessels, intestine, kidneys and testis [5]. As a result of SARS-CoV-2 infection, virus attachment to ACE2 receptors located on the surface of cardiac epithelial cells leads to the direct harm to the myocardium and subsequent dysfunction, potentially contributing to the overall damage—Figure 1. The significant presence of ACE2 in cardiomyocytes, fibroblasts, endothelial cells, epicardial adipocytes, and smooth muscle cells further reinforces the theory of viral injury occurring directly [6]. The presence of cardiovascular complications in individuals with COVID-19 leads to a more unfavourable prognosis, underscoring the significance of early detection and the implementation of effective therapeutic approaches. Patients who already have underlying conditions like cardiovascular disease face a particularly elevated risk of illness and death resulting from this viral infection. Given the compelling evidence suggesting that myocardial damage worsens the severity of COVID-19, healthcare professionals should prioritize cardiac management. Moreover, multiple studies have shown that COVID-19 can worsen existing cardiovascular conditions and induce new cardiovascular injuries [7,8]. Furthermore, the long-term consequences of COVID-19 on cardiovascular health remain a major global concern.

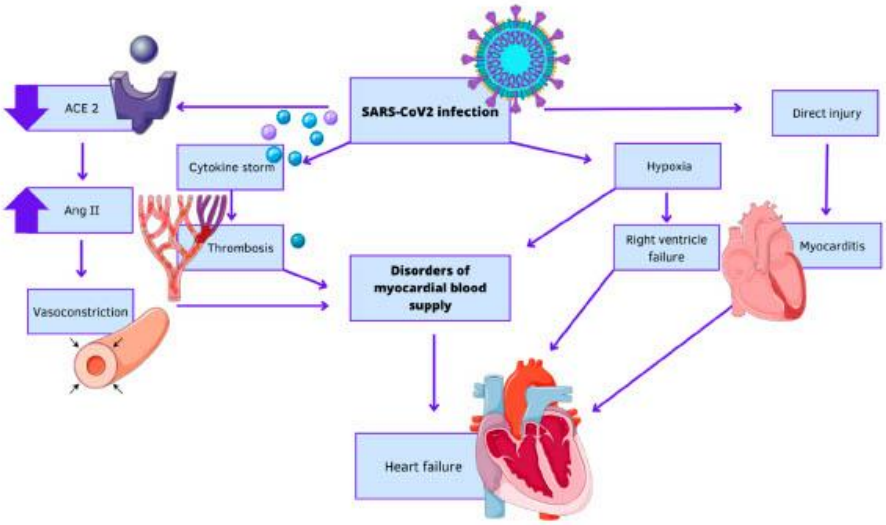


**Figure 1.** Mechanism of development COVID-19-induced heart failure. The figure was partly generated using Servier Medical Art, provided by Servier, licenced under a Creative Commons Attribution 3.0 unported licence.

## 2. COVID-19 and Heart Failure

Heart failure (HF) remains a major clinical and public health concern. This condition is also known as the cardiovascular epidemic of the 21st century [9]. This finding has been reinforced by the observation of an exponential increase in hospitalisations for HF. Current estimates indicate that HF affects more than 64 million people around the world [10]. In 2021, the world's largest scientific organisations proposed a consensus on the universal definition and classification of HF [11]. HF was defined as a clinical syndrome with symptoms due to a structural and/or functional abnormality of the heart, confirmed by elevated levels of natriuretic peptides and/or objective evidence of pulmonary or systemic congestion. HF was divided into three categories according to left ventricular ejection fraction (EF): HF with reduced EF (HFrEF), slightly reduced (HFmrEF), and preserved EF (HFpEF), according to the ranges of EF <40%, 41–49%, and 50%, respectively. Furthermore, a new unit was introduced, i.e., HF with EF improvement, which was defined as HF with baseline EF <40% with a 10-point increase in EF from baseline value and a second measurement of EF > 40% [12]. Trends in HF show an overall increase in HF prevalence; however, when data are analysed according to EF, the prevalence of HFpEF has been observed to increase, but it is stable or even decreases for HFrEF [13]. Understanding the pathophysiological mechanism leading to heart failure is crucial for the selection of appropriate therapeutic options. After myocardial damage (e.g., myocardial infarction, infection), cellular and neurohumoral processes occur, the consequence of which is the activation of the sympathoadrenergic system and renin–angiotensin–aldosterone. This phenomenon leads to adaptive mechanisms accompanied by volume overload, tachycardia, shortness of breath, and further deterioration of cellular function [14].

Inflammation is an important factor in the development of HF. Previous research has shown that inflammation contributes to the pathogenesis of HFrEF [15–17]. However, the contradictory results of several trials of anti-inflammatory drugs led to the conclusion that inflammation played a role in the development of HFrEF, but it is more likely not to be a primary cause [18]. In contrast, inflammation is believed to promote the development of HFpEF [19]. Several studies have shown that increased levels of inflammatory molecules such as C-reactive protein (CRP), tumour necrosis factor-alpha (TNFα), interleukin-1 (IL-1), growth differentiation factor 15 (GDF15), soluble ST2, and pentraxin-3 are more noticeable in HFpEF than in HFrEF [20–23]. In the work of Chuda-Wietczak, the authors showed that elevated CRP (>2.38 µg/mL, OR = 2.93, 95% CI = 1.31–6.54, $p = 0.007$) was an independent prognostic factor for adverse clinical events (CE) in the population with HF [24]. Myocarditis is often considered a potential cause of HF in patients with COVID-19. However, some reports have indicated that myocarditis is not commonly observed in severe cases of COVID-19 and it tends to be mild [25,26].

The relationship between COVID-19 and heart failure is complex. Pro-inflammatory cytokines triggered by SARS-CoV-2 may indirectly lead to cardiac damage. Several clinical studies on COVID-19 patients reported significantly elevated inflammatory biomarkers in circulation, including interleukin (IL)-2, IL-6, IL-7, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), tumour necrosis factor-α (TNF-α), interferon-γ inducible protein (IP)-10, CRP, ferritin, and procalcitonin [7,27]. Although triggered by local infection in the lungs, increased systemic levels of these inflammatory cytokines activate inflammatory and maladaptive remodelling pathways in multiple organs, including the heart.

The COVID-19 outbreak has an impact on HF management, with a decrease in hospitalisation for HF during the outbreak, leading to an increase in HF mortality. HF can be a consequence of COVID-19-related myocardial damage. HF history is a risk factor for more serious clinical cases of COVID-19. Patients with HF are more likely to develop a myocardial injury. The history of HF has also been found to be associated with an increased risk of hospitalisation and a severe clinical course in patients with COVID-19. Observation studies in patients hospitalised with COVID-19 detected vascular damage based on troponin levels and defined it as an increase greater than the normal 99 percentile. Blood

pressure levels increased by 8–12% in unselected cases of COVID-19, increased from 23% to 33% in critically ill patients, and increased further when considered in patients with heart disease [28–30]. Some studies have also evaluated plasma concentrations of N-terminal-pro-brain natriuretic peptides (NT-proBNP) and have shown that these concentrations are higher in patients with myocardial injuries, although these are not independently associated with the results [30,31]. Natriuretic peptides have been found to be elevated in patients with COVID-19, even in the absence of heart failure. Due to this factor, the diagnosis of HF can be challenging in this group of patients. In the study of Bergami et al., the authors included COVID-19 patients and demonstrated that 53.4% had elevated BNP levels. High BNP levels were also strongly associated with an increased risk of AHF (OR 19.9; 95% CI 8.6–45.9; $p < 0.001$), a correlation that persisted both in patients with and without a prior cardiovascular disease history ($p$ for interaction = 0.29). Subjects with increased BNP also had a higher likelihood of developing ARF (OR 2.7; 95% CI 2.1–3.6; $p$-value < 0.001), even in the absence of AHF (OR 3.00; 95% CI 2.20–4.1; $p$-value < 0.001) [32]. This finding supports the recommendation to regularly utilize BNP testing for all COVID-19 patients admitted to the hospital, regardless of their previous cardiovascular disease history.

Cardiovascular complications, including HF, have been associated with other viral respiratory diseases. Infection with respiratory syncytial virus (RSV) infection frequently results in the onset of HF due to pre-existing cardiopulmonary and immunoprophylaxis conditions [33]. The influenza virus is known to have significant impacts on inflammatory processes and is a common trigger for cardiovascular diseases [34]. The potential relationship between influenza infection and the emergence of HF involves various pathophysiological disruptions. These include hypoxemia, activation of neuroendocrine and sympathetic systems, volume overload due to cardio-renal injury, direct injury to cardiomyocytes, and concurrent hyperinflammation. These factors interact with each other, contributing to the progression of HF [35]. According to a study conducted by Kytomaa et al., the analysis of community surveillance data was utilized to examine the occurrence of myocardial infarction (MI) and hospitalizations for heart failure in relation to monthly influenza activity. The findings demonstrated that a 5% monthly rise in influenza activity was linked to a 24% increase in hospitalizations for heart failure, with an incidence rate ratio (IRR) of 1.24 (95% CI, 1.11–1.38; $p < 0.001$) [36]. In contrast to the COVID-19 pandemic, a decrease of 50% in heart failure hospitalizations has been observed since the first diagnosed case of COVID-19 [37]. A similar downward trend has been observed in acute cardiovascular hospitalizations, with a significant decrease in the daily hospitalization rate throughout March 2020 (at a rate of −5.9% per day, ranging from −7.6% to −4.3%, $p < 0.001$) [38]. These reductions occurred despite a significant increase in mortality (up to 90%) attributed to cardiovascular diseases during this period, along with a temporary doubling of out-of-hospital cardiac arrest incidences [39]. This suggests that the decrease in hospitalizations can largely be attributed to patients' fear of seeking healthcare in medical facilities due to concerns about contracting the virus. This fear is further supported by the widespread adoption of physical distancing and isolation measures.

The clinical manifestations of the myocardial injury caused by SARS-CoV-2 include arrhythmia and sudden cardiac death, pulmonary embolism, acute coronary syndromes, myocarditis, acute heart failure, and cardiogenic shock [40]. Furthermore, it should be noted that distant cardiovascular complications can also occur in patients with mild or non-symptomatic courses of COVID-19.

Several studies have shown the adverse effects of COVID-19 infection on pre-existing cardiovascular disease. In a study by Inciardi et al., the authors compared the clinical presentations and outcomes of patients ($n$ = 99) with and without cardiac disease hospitalised for COVID-19. Among cardiac patients, 40% had a history of heart failure, 36% had atrial fibrillation, and 30% had coronary artery disease. Mortality was higher in patients with cardiac disease compared to the others [41]. Patients may have experienced acute heart failure (AHF) in addition to chest pain, suggesting myocardial ischemia or myocardial ischemia and palpitations. After ARDS and sepsis, HF was the leading cause of death in

113 deaths from COVID-19 [42]. Subsequent studies have also shown a worse prognosis in patients with COVID-19 who had known cardiovascular disease [43–46]. In the study of Bhatt et al., data from 1,212,153 HF patients were analysed. The authors revealed that hospitalisation with COVID-19 was associated with greater odds of in-hospital mortality as compared to hospitalisation with acute HF. In total, 24.2% of patients hospitalised with COVID-19 died in hospital compared to 2.6% of those hospitalised with acute HF [47]. Sokolski et al. compared the outcomes of hospitalised COVID-19 patients with HF and patients with other cardiovascular diseases. This study demonstrated an increased risk of in-hospital death in patients with HF [48]. Other research studies confirmed a higher risk of death in patients with COVID-19 [49–52].

Patients who have been infected with SARS-CoV-2 may also be at risk of developing heart failure. Rey et al. collected data from 3080 patients with confirmed infection and 30 days after infection. Patients with COVID-19 had a significant incidence of AHF, which was associated with very high mortality rates. Furthermore, patients with a history of chronic heart failure (CHF) were prone to developing acute decompensation after a diagnosis of COVID-19 [53]. The study of Zaccone et al. has shown that COVID-19 could be an independent risk factor for the development of HFpEF [54]. In another meta-analysis, the authors demonstrated acute HF as a frequent complication of COVID-19 infection, associated with a higher risk of mortality in the short term [55].

In our study, we enrolled patients who recovered from COVID-19 three to six months after their confirmed diagnosis. These patients were divided into two groups: study group presented with worse oxygen uptake (VO2) [%VO2pred <80%; $n = 47$ at a median age of 49 years, median VO2max 17 mL/kg/min]; and a control group with a median age 55 years who had VO2pred <80% [73 patients, median 23 mL/kg/min]. There was a higher proportion of men and a greater percentage of total body water content (TBW%) in the study group compared to the control group (53% vs. 29%, $p = 0.007$, and 52.67% (±6.41) vs. 49.89% (±4.59), $p = 0.02$, respectively). The group with %VO2pred <80% presented with significantly lower late diastolic fill velocity (A), global peak systolic strain (GLPS), and annular tricuspid plane systolic excursion (TAPSE) compared to the control group [median 59.5 (IQR: 50.0–71.0) vs. 70.5 (IQR: 62.0–80.0) cm/s, $p = 0.004$; 19.34 (±1.72) vs. 20.10 (±1.35) %, $p = 0.03$; 21.86 (±4.53) vs. 24.08 (±3.20) mm, $p = 0.002$; respectively]. Multiple logistic regression analysis indicated that velocity (A) and male gender were independently associated with %VO2pred [OR 0.40, 95% CI 0.17–0.95, $p = 0.03$; OR 2.52, 95% CI 1.07–5.91, $p = 0.03$; respectively]. Lower velocity (A), TAPSE, GLPS and hydration status are related to limited exercise tolerance after COVID-19 in patients with normal left ventricular ejection fraction [56]. Based on these results, patients with long-COVID without heart failure diagnosis may have worse echocardiographic parameters of diastolic dysfunction. Ergospirometry can be useful in assessing the risk of developing heart failure in this group of patients. Further analyses are warranted. Other studies have also shown echocardiographic abnormalities in survivors of COVID-19 [57,58].

Currently, the validity of cardiovascular screening after COVID-19 has not been confirmed, and there are no established guidelines for such diagnostics. However, some studies suggest that the screening may be useful in patients with post-acute COVID-19 syndrome [59,60]. Until appropriate recommendations are made, diagnosis procedures must be individualised based on the course of the acute phase and clinical symptoms reported or submitted after COVID-19. Clinical phenomena are the criteria for determining the recommended test panel. The most common diseases reported to patients after infection include exercise intolerance, which usually requires a different diagnosis (cardiac disease, pulmonary disease, muscle loss, or mental illness) [57]. Table 1 summarises the results of the studies mentioned above.

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

| Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|
| [41] Inciardi R.M. et al. (2020) | 99 | Single-centre | Out of 99 patients, 53 had cardiac disease, and 40% of them had a history of heart failure. Patients with cardiac disease had a higher mortality rate compared to those without cardiac disease (36% vs. 15%). Furthermore, patients with cardiac disease had a higher prevalence of thromboembolic incidents and septic shock compared to those without cardiac disease (23% vs. 6% and 11% vs. 0%, respectively). |
| [42] Chen T et al. (2020) | 274 | Retrospective case series | Patients who died from COVID-19 had higher levels of troponin I, NT-proBNP, and D-dimer than those who recovered. Additionally, parameters such as alanine aminotransferase, aspartate aminotransferase, creatinine, creatine kinase, and lactate dehydrogenase were higher in deceased patients. Patients who died from COVID-19 were more likely to develop complications such as heart failure (41/83; 49%) or acute cardiac injury (72/94; 77%), and had a higher incidence of acute respiratory distress syndrome (113; 100%), type I respiratory failure (18/35; 51%), sepsis (113; 100%), alkalosis (14/35; 40%), hyperkalemia (42; 37%), acute kidney injury (28; 25%) and hypoxic encephalopathy (23; 20%). Cardiovascular complications were more common in patients with cardiovascular comorbidity. Acute cardiac injury and heart failure were more common in patients who died of COVID-19. These were independent of a history of cardiovascular disease. |
| [43] Tomasoni D. et al. (2020) | 692 | Prospective multicentre cohort study | Patients diagnosed with heart failure were more likely to have complications such as acute heart failure (33.3% vs. 5.1%), acute renal failure (28.1% vs. 12.9%), multiorgan failure (15.9% vs. 5.8%) or sepsis (18.4% vs. 8.9%). A history of heart failure indicates a higher risk of death from COVID-19 infection (41% vs. 21%). |
| [44] Alvarez-Garcia J. et al. (2020) | 6439 | Retrospective analysis | Patients with diagnosed heart failure were more likely to require mechanical ventilation (22.8% vs. 11.9%) and had a higher mortality rate (40.0% vs. 24.9%). Patients with previous heart failure had comparable results, regardless of the ejection fraction of left ventricle or the use of renin–angiotensin–aldosterone inhibitor. |
| [46] Salah H.M. et al. (2022) | 257,075 | Cohort study, multicentre | Hospitalization for COVID-19 was related to increased risk of heart failure by 45%. Heart failure occurred more often in patients under 65 years of age, white, or who had been diagnosed with cardiovascular disease. |

**Table 1.** *Cont.*

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [47] | Bhatt A.S. et al. (2021) | 132,312 | Cohort study | Patients who were previously diagnosed with heart failure and were hospitalized due to COVID-19 had a significantly higher mortality rate (24.2%) compared to those who were hospitalized for acute heart failure (2.6%). Additionally, male gender, advanced age, morbid obesity, and diabetes were identified as risk factors associated with poorer outcomes and higher mortality during hospitalization. |
| [48] | Sokolski M. et al. (2021) | 1282 | Cohort study, multicentre, retrospective | Patients with a history of heart failure had a mortality rate of 36%, which was higher than the mortality rate of patients without a history of heart failure (23%). During hospitalization, 15% of patients experienced an acute heart failure incident, and 40% of these incidents were new cases. Patients who experienced acute heart failure during hospitalization had a higher mortality rate of 48% compared to non-heart failure patients (23%). |
| [49] | Greene S.J. et al. (2022) | 99,052 | Retrospective, cohort study | Patients with worsening heart failure with reduced ejection fraction (HFrEF) and those without HFrEF exacerbation had a higher 30-day mortality compared to patients without concomitant heart failure. Among patients diagnosed with HFrEF who tested positive for COVID-19, there was a higher risk of death within 30 days and an increased likelihood that their heart failure worsened. Additionally, patients who presented to healthcare facilities as outpatients had a higher mortality rate. |
| [50] | Kim H.J. et al. (2022) | 212,678 | Retrospective, cohort study | COVID-19 infection increases the risk of developing new-onset heart failure and exacerbating pre-existing heart failure. Patients with a history of heart failure had a poorer prognosis, a higher mortality rate (17.71% vs. 9.28%), and greater risk of developing severe complications compared to patients without heart failure. However, mechanical ventilation or admission to the intensive care unit was not required more often in patients with a history of HF. In contrast, COVID-19 infection was not found to be more frequent in patients with heart failure. |
| [52] | Yonas E. et al. (2021) | 21,640 | Analysis | Patients who have been diagnosed with heart failure and develop COVID-19 are more likely to require hospitalisation (odds ratio [OR] 2.37), experience poor outcomes (OR 2.86), and have an increased risk of death (OR 3.46). |

**Table 1.** *Cont.*

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [53] | Rey J.R. et al. (2020) | 3080 | Prospective cohort study | Patients diagnosed with chronic heart failure (CHF) have a higher frequency of acute heart failure (AHF) episodes (11.2%) than patients without CHF (2.1%), and N-terminal pro brain natriuretic peptide levels are elevated. Additionally, CHF is associated with higher mortality rates (48.7%) than non-HF patients (19%). Arrhythmias during hospital admission and CHF were found to be the main factors contributing to the development of AHF. Patients who develop AHF have a higher mortality rate (46.8% vs. 19.7%). Discontinuation of guideline-directed medical therapy, including beta-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, was also associated with increased mortality rates. |
| [54] | Zaccone G. et al. (2021) | | Analysis | In patients hospitalised for COVID-19 infection, the incidence of HF comorbidity is (4–16%), this may be due to a shared cardiometabolic risk profile and comorbidities such as hypertension, diabetes, obesity and chronic kidney disease, which increase the risk of severe course of COVID-19 and are also risk factors of HFpEF. COVID-19 infection can induce acute decompensation of HF in patients with pre-existing HFpEF and in those with subclinical diastolic dysfunction. In the acute and subacute phases of COVID-19, impaired diastole (rather than systole), pulmonary hypertension, and right ventricular dysfunction can be observed. In 78% of patients in the chronic phase of COVID-19, inflammation and myocardial fibrosis are observed. |
| [55] | Zuin M. et al. (2022) | 1,628,424 | Retrospective | Cardiovascular disease and structural heart changes are more common in patients after recovery from COVID-19. Additionally, patients who underwent COVID-19 were more likely to experience an episode of HF. The overall incidence of HF after COVID-19 infection was 0.4–2%. After 9.2 months, the frequency was 1.8–2.04. Moreover, an increased risk of HF was caused by older age and hypertension. |

Table 1. *Cont.*

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [56] | Gryglewska-Wawrzak K. et al. (2022) | 120 | Single-centre | The group of study participants with %VO2pred < 80% had a significantly higher proportion of men and a higher total body water (TBW%) compared to the control group (53% vs. 29% and 52.67% (±6.41) vs. 49.89% (±4.59), respectively). Individuals who presented with limited exercise capacity after COVID-19 infection demonstrated lower tricuspid annular plane systolic excursion (TAPSE), global peak systolic strain (GLPS), and late diastolic filling (A) velocity [21.86 mm (±4.53) vs. 24.08 mm (±3.20); 19.34% (±1.72) vs. 20.10% (±1.35)%; a median of 59.5 cm/s vs. 70.5 cm/s) compared to the control group. |

## 3. Diagnosis of Heart Failure in Patients after COVID-19

### 3.1. Clinical Examination

Thorough subjective and physical examinations allow one to raise suspicion of the disease and plan further diagnostic procedures. The subjective examination is the first examination that, when properly conducted, allows one to propose a correct initial diagnosis of the disease in many patients. For patients who present symptoms of heart failure for the first time to a primary care physician or cardiology clinic, the physician first assesses the likelihood of a disease based on the history of coronary artery disease, high blood pressure, and other diseases and conditions that can cause heart failure. The doctor then examines the patient for signs of heart failure [61,62].

### 3.2. Laboratory Tests

The following parameters are of particular importance in the diagnosis of heart failure [12]:

1. concentration of natriuretic peptides in plasma—to exclude HF: in a patient without acute worsening of symptoms, HF is unlikely when BNP < 35 pg/mL (<105 pg/mL in atrial fibrillation), NT-proBNP < 125 pg/mL (<365 pg/mL in atrial fibrillation);
2. arterial blood gas analysis for detection of respiratory failure;
3. serum troponin for detection of acute coronary syndrome (ACS);
4. blood urea nitrogen, serum creatinine, electrolytes—for the detection of renal dysfunction;
5. full blood count—anemia may exacerbate or cause CHF;
6. transferrin, ferritin, signs of iron deficiency, most often of a functional nature—reduced transferrin iron saturation; a decrease in ferritin usually occurs only with absolute iron deficiency (it may not occur in the presence of inflammation);
7. inflammatory cytokines (C-reactive protein, procalcitonin)—for the diagnosis of infection;
8. increased activity of aminotransferases and lactate dehydrogenase (LDH), increased concentrations of bilirubin in plasma—in patients with venous stasis in the systemic circulation, with hepatomegaly;
9. the concentration of thyroid stimulating hormone (TSH), because thyroid disease can mimic or worsen the symptoms of HF;
10. D-dimer—when pulmonary embolism (PE) is suspected.

There are established guidelines for managing outpatients with suspicion of PE [63], based on clinical probability assessment and D-dimer dosage. Outcome studies have shown that the 3-month thromboembolic risk is <1% in patients with low or intermediate clinical probability and D-dimer < 500 ng·mL$^{-1}$ who are left untreated [64]. The adjust-PE study has demonstrated that the D-dimer level adjusted to patient age, with higher thresholds in older patients (age × 10 ng·mL$^{-1}$), can safely rule out PE [65]. Hypercoagulability and the need to prioritise coagulation markers for prognostic abilities have been highlighted in

COVID-19. In a meta-analysis, the authors included 113 studies ($n$ = 38,310) and showed that higher D-dimer levels provide prognostic information useful for clinicians to assess early COVID-19 patients at risk for disease progression and mortality outcomes [66].

### 3.3. Electrocardiogram (ECG)

The ECG usually reveals features of the underlying disease—ischemic heart disease, arrhythmias or conduction disorders, hypertrophy, or overload [67].

### 3.4. Chest Radiograph

The chest radiograph generally reveals enlargement of the heart (except in most cases of hyperkinetic states and diastolic insufficiency), signs of venous congestion in the pulmonary circulation [68].

### 3.5. Echocardiography

1. Left ventricular systolic function—by analysing segmental and global left ventricular contractility and left ventricular ejection fraction (LVEF) measurement (Simpson method; <40% indicates significant left ventricular systolic dysfunction; values 41–49% are considered the so-called grey zone and one of the diagnostic criteria HFmrEF—a complete differential diagnosis of noncardiac causes of symptoms is necessary, as in HFpEF) [12].
2. Left ventricular diastolic function—transmitral E/A ratio and E velocity deceleration time (DT), e' velocity (average and absolute value of septal and lateral side) of the mitral annulus by pulsed tissue Doppler, E/e' ratio, and the estimate of systolic pulmonary artery pressure (sPAP) derived from tricuspid regurgitation (TR) velocity [69].
3. Anatomical abnormalities, hypertrophy, dilation of the heart chambers, valvular defects, congenital defects. Additional evaluation of many parameters of cardiac structure and function is of particular importance in differential diagnosis, especially with LVEF <40%. In some cases (e.g., poor imaging conditions on transthoracic examination, suspected prosthetic valve dysfunction, detection of a thrombus in the left ear in patients with atrial fibrillation, diagnosis of bacterial endocarditis or congenital defects), transoesophageal echocardiography is indicated [70].
4. Signs of PE—dilation of the right ventricle (RV), pulmonary ejection acceleration time <60 ms with a peak systolic tricuspid valve gradient < 60 mmHg [63]. Echocardiographic examination is not mandatory as part of the routine diagnostic workup in haemodynamically stable patients with suspected PE. In case of suspected high-risk PE, the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of hemodynamic instability [71].

### 3.6. Computed Tomographic Pulmonary Angiography (CTPA)

CTPA is the first-line imaging technique in patients with suspected PE and is indicated as a class IC procedure for individuals with a high suspicion of PE, even in cases of hemodynamic instability. In patients with low or moderate clinical probability, a correct CTPA result can be sufficient to rule out the diagnosis of PE without the need for additional testing (class IA) [63].

### 3.7. Compression Ultrasonography (CUS)

CUS is a relevant tool for diagnosing deep vein thrombosis (DVP). This condition is a major medical problem that accounts for most cases of pulmonary embolism [72].

### 3.8. Cardiopulmonary Exercise Testing (CPET)

CPET is a relevant tool in patients with long-COVID. This examination is helpful in the case of a discrepancy between the severity of symptoms and the objective parameters of the severity of the disease, and when distinguishing between cardiac and pulmonary causes

of dyspnea [73]. In one meta-analysis, the authors demonstrated that exercise capacity was reduced more than 3 months after SARS-CoV-2 infection among individuals with long-COVID symptoms compared with individuals without symptoms [74].

Figure 2 demonstrates proposed management in long-COVID patients with suspected heart failure.

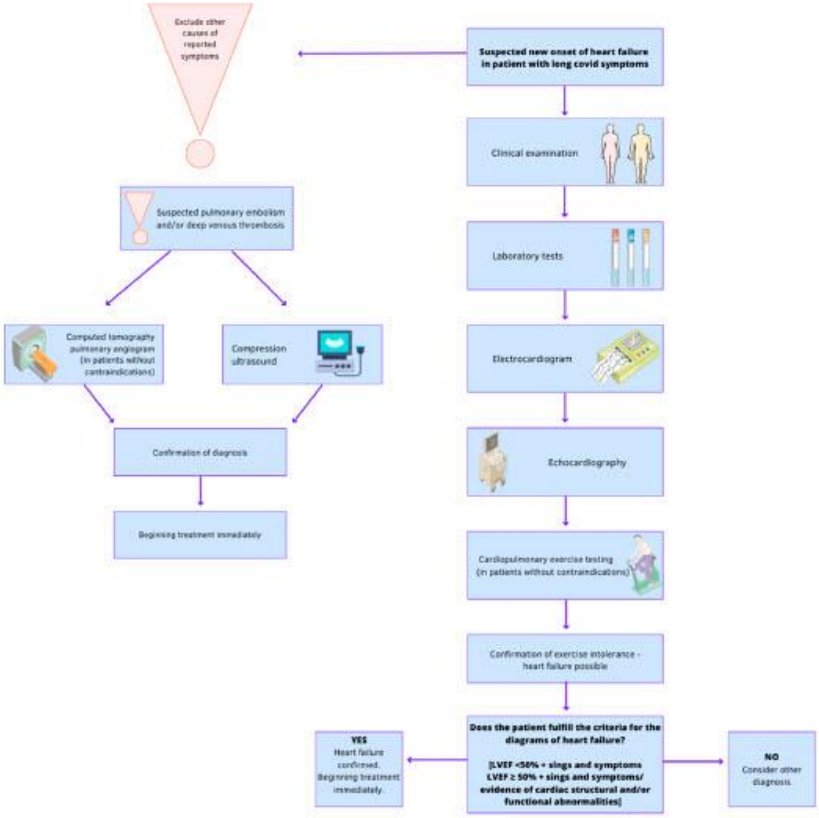


**Figure 2.** Management in long-COVID patients with suspected heart failure. The figure was partly generated using Servier Medical Art, provided by Servier, licenced under a Creative Commons Attribution 3.0 unported licence; one of the icons was from Flaticom.com (accessed on 18 April 2023).

## 4. Treatment of Heart Failure after COVID-19

The management of HF in patients with or after COVID-19 should be performed according to established guidelines and protocols. The pharmacotherapy management for heart failure depends on the haemodynamic status. During the pandemic, there were hypotheses that angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or angiotensin receptor neprilysin inhibitors (ARNI) may affect mortality in patients with COVID-19, theoretically due to interaction with the bradykinin pathway. Several scientific societies recommend that treatment with RAAS inhibitors (ACEi/ARB/ARNI) should not be discontinued in patients diagnosed with COVID-19 [75]. Interruption is associated with an increased mortality risk [76–78]. Safety and efficacy of using sodium-

glucose co-transporter 2 inhibitors (SGLT2i) in case of COVID-19 is still debatable. Zhu et al. conducted a meta-analysis in patients with diabetes mellitus and showed that the use of SGLT2i before COVID-19 infection is associated with lower adverse outcomes [79]. More research is needed in patients with HF. Beta-receptor blockers should be used with caution with patients treated with antiviral agents due to the risk of hypotension and bradycardia. Currently, there is no evidence that the four beta-blockers approved for HF treatment (metoprolol, bisoprolol, carvedilol, or nebivolol) are preferred, but experimental studies have shown that carvedilol may offer unique anti-cytokine properties [80]. Currently, there is contradictory evidence regarding the role of mineralocorticoid receptor antagonists (MRA). In a research study, the authors demonstrated that, in patients with COVID-19, MRA treatment had an overall positive impact on all-cause mortality and clinical improvement, most probably through a direct anti-inflammatory effect [81]. In another study, SARS-CoV-2-induced endothelial injury was abrogated by the spironolactone [82]. In a systematic review, an association between MRA therapy and mortality in patients infected with SARS-CoV-2 was explored [83].

## 5. COVID-19 and Coagulopathy

COVID-19 is primarily considered a respiratory infection, but there is increasing evidence of multi-organ complications of the disease. Compared to other common respiratory viral infections, patients with COVID-19 had a higher incidence and severity of blood clotting, usually associated with higher levels of D dimer, C-reactive protein, P-selectin and fibrinogen. The hypercoagulation state of COVID-19 infection is associated with severe inflammatory reactions, cytokine storm, endothelial damage, and clinical complications [84,85]. The mechanisms of coagulopathy are complex in COVID-19. It may involve the common pathways documented in other viral diseases and hospitalized patients, such as endothelium cell damage by viral antigens, upregulation of Toll-like receptors and von Willebrand factors, causing an uncontrolled coagulation similar to disseminated intravascular coagulopathy (DIC) with excess fibrin clot formation. When these fibrin clots are degraded by the body's own anticoagulant system, fibrin degradation products are produced, including D-Dimer, which is commonly tested in laboratories [86].

Furthermore, the pro-inflammatory state promotes further thrombogenesis by inhibiting anticoagulation processes, such as thrombomodulin, endothelial cell protein C, and the TF pathway inhibitor. Eventually, fibrinolysis is inhibited by the release of plasminogen activator inhibitor-1 (PAI-1) from endothelial cells during inflammation [87].

Due to the unique complications described above, the prolonged anticoagulation in patients with thrombosis during COVID-19 infection should be considered. Lachant et al. demonstrated that chronic anticoagulation at the time of infection may protect against thrombotic complications and decrease disease severity [88]. In one multicentre, randomized trial, patients hospitalised with COVID-19 at increased risk for VTE were randomly assigned (1:1) to receive, at hospital discharge, rivaroxaban 10 mg/day or no anticoagulation for 35 days. In individuals with a high risk of complications who were discharged from the hospital following COVID-19, administering rivaroxaban at a dose of 10 mg per day for a duration of 35 days improved clinical outcomes compared with no extended thromboprophylaxis [89].

Won et al. conducted a study in which the autopsy lungs of COVID-19 patients exhibited severe coagulation abnormalities, immune cell infiltration, and platelet activation [90]. In one small study, the authors examined the lungs of patients who died from COVID-19 and compared them with seven lungs obtained during autopsy from patients who died from ARDS secondary to influenza A(H1N1) infection and uninfected control lungs. Autopsy of the COVID-19 has demonstrated extensive endothelial injury, vascular thrombosis with microangiopathy, occlusion of the alveolar capillaries, and signs of neo-angiogenesis. Additionally, capillary microthrombosis was nine times more frequent in COVID-19 compared to influenza [91]. In a series of autopsy of COVID-19 patients in Germany, 58% of patients with blood thromboembolism did not suspect thromboembolism before death [92].

Many studies have focused on the risk factors for the development of coagulopathy in COVID-19 and determining its relationship with the severity of the infection. A meta-analysis showed an association between cardiac injury in COVID-19 and developing coagulopathy [93]. Jin et al. demonstrated that coagulation dysfunction was frequent in Chinese COVID-19 patients. Non-survivors had significantly higher levels of D-dimer, prolonged prothrombin time (PT), and decreased platelet counts compared to survivors [94]. Similar results were also obtained in another research [95]. The study of Zhu demonstrated a high prevalence of coagulopathy in patients with severe COVID-19 [96]. Other meta-analyses confirmed the association between coagulopathy and a poor prognosis of SARS-CoV-2 infection [97,98]. In the Agarwal meta-analysis, 28 studies included 6053 patients with SARS-CoV-2 infection. The authors demonstrated that venous thromboembolic events in COVID-19 were associated with male gender [99]. Another study showed that immune thrombocytopenia (ITP) secondary to SARS-CoV-2 infection was more prevalent in men (54.8%) [100].

One of the potential severe complications in COVID-19 is PE [101,102]. Roncon et al. performed a systematic review including data from 7178 patients. They revealed that the incidence of acute PE among COVID-19 patients was higher in intensive care unit (ICU) patients compared to those hospitalised in general wards [103]. Other studies confirmed that PE is a significant complication of COVID-19, especially in ICU patients [104,105].

The rate of recurrent or progressive PE despite anticoagulant therapy is considerable. In one study, patients with confirmed PE underwent CTPA follow-up. Complete thrombus resolution was observed in 60% of the cohort. Residual thrombosis was visible in 30% of the patients [106]. In another study, complete resolution of thrombus was observed in 72% patients after a mean period of 48 days of confirmed diagnosis of PE [107]. Table 2 summarises the results of the studies mentioned above.

**Table 2.** The characteristics of included meta-analyses.

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [93] | Bansal A. et al. (2020) | 3175 | Meta-analysis | Cardiac injury in patients with a COVID-19 was associated with higher risk of mortality (risk ratio [RR]:7.79; 95% confidence interval [CI]: 4.69–13.01; $I^2$ = 58%), admission to the intensive care unit (ICU) (RR: 4.06; 95% CI: 1.50–10.97; $I^2$ = 61%), mechanical ventilation (RR: 5.53; 95% CI: 3.09–9.91; $I^2$ = 0%), and developing coagulopathy (RR: 3.86; 95% CI: 2.81–5.32; $I^2$ = 0%). |
| [94] | Jin S. et al. (2020) | 4889 | Meta-analysis | Severe patients had significantly higher D-dimer levels and prolonged prothrombin time (PT) compared with non-severe patients. Non-survivors had significantly higher D-dimer levels, prolonged PT, and decreased platelet count (PLT) compared to survivors. In total, 6.2% (95% CI: 2.6–9.9%) of COVID-19 patients were complicated by disseminated intravascular coagulation (DIC), in which the log risk ratio in non-survivors was 3.267 (95% CI: 2.191–4.342, Z ¼ 5.95, $p < 0.05$) compared with that in survivors. |

Table 2. *Cont.*

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [95] | Polimeni A. et al. (2021) | 6439 | Meta-analysis | D-dimer was significantly lower in COVID-19 patients with non-severe disease than in those with severe (standardized mean difference [SMD] −2.15 [−2.73–−1.56], $I^2$ 98%, $p < 0.0001$). D-dimer in survivors was lower compared to non-survivors (SMD −2.91 [−3.87–−1.96], $I^2$ 98%, $p < 0.0001$). Platelet count showed higher levels of mean PLT in non-severe patients than those observed in the severe group (SMD 0.77 [0.32–1.22], $I^2$ 96%, $p < 0.001$). |
| [96] | Zhu J. et al. (2021) | 6492 | Meta-analysis | Patients with severe disease showed a significantly lower platelet count (weighted mean difference [WMD]: −16.29 × 109/L; 95% CI: −25.34–7.23) and shorter activated partial thromboplastin time (WMD: 0.81 s; 95% CI: −1.94–0.33) but higher D dimer levels (WMD: 0.44 µg/mL; 95% CI: 0.29–0.58), higher fibrinogen levels (WMD: 0.51 g/L; 95% CI: 0.33–0.69) and longer prothrombin time (PT; WMD: 0.65 s; 95% CI: 0.44–0.86). The patients who died showed significantly higher D dimer levels (WMD: 6.58 µg/mL; 95% CI: 3.59-9.57), longer PT (WMD: 1.27 s; 95% CI: 0.49–2.06) and lower platelet count (WMD: −39.73 × 109/L; 95% CI: 61.99–−17.45) than patients who survived. |
| [97] | Zhang A. et al. (2020) | 2277 | Meta-analysis | The level in severe cases was lower than in mild cases, while the levels of PT, D-Dimer and fibrinogen were higher than those in mild cases ($p < 0.05$). The PT of the ICU patients was significantly longer ($p < 0.05$) than that of the non-ICU patients. PT and D-dimer were higher in non-survivors, PLT was lower than that of survivors ($p < 0.05$). |
| [98] | Zhang X. et al. (2020) | 3952 | Meta-analysis | Patients with severe symptoms exhibited higher levels of D-dimer, PT and fibrinogen than patients with less severe symptoms (SMD 0.83, 95% CI 0.70–0.97, $I^2$ 56.9%; SMD 0.39, 95% CI: 0.14–0.64, $I^2$ 79.4%; and SMD 0.35, 95% CI 0.17–0.53, $I^2$ 42.4%, respectively). |
| [99] | Agarwal G. et al. (2022) | 6053 | Meta-analysis | Patients with COVID-19 with venous thromboembolic events (VTE) had higher leukocyte counts and higher levels of D-dimer, C-reactive protein, and procalcitonin. |

Table 2. *Cont.*

| | Study (Year) | Number of Patients | Design | Findings |
|---|---|---|---|---|
| [100] | Alharbi M.G. et al. (2022) | 55 | Meta-analysis | Immune thrombocytopenia (ITP) secondary to COVID-19 infection was slightly more common among males (54.8%) than females. |
| [103] | Roncon et al. (2020) | 7178 | Meta-analysis | Among patients with COVID-19 hospitalized in general wards and ICU, the pooled in-hospital incidence of pulmonary embolism (PE) (or lung thrombosis) was 14.7% of cases (95% CI: 9.9–21.3%, $I^2 = 95.0\%$, $p < 0.0001$) and 23.4% (95% CI:16.7–31.8%, $I^2 = 88.7\%$, $p < 0.0001$), respectively. Segmental/sub-segmental pulmonary arteries were more frequently involved compared to main/lobar arteries (6.8% vs. 18.8%, $p < 0.001$). |
| [104] | Ng J. J. et al. (2020) | 1182 | Meta-analysis | The weighted average incidence of PE in COVID-19 patients admitted to the ICU was 11.1% (95% CI 7.7% to 15.7%, $I^2 = 78\%$, Cochran's Q test $p < 0.01$). |
| [105] | Gong X et al. (2022) | 10,367 | Meta-analysis | The cumulative incidence of PE in patients with COVID-19 was 21% (95% confidence interval [95% CI]: 18–24%; $p < 0.001$), and the incidence of pulmonary embolism in ICU and non-ICU patients was 26% (95% CI: 22–31%; $p < 0.001$) and 17% (95% CI: 14–20%; $p < 0.001$), respectively. |

## 6. Conclusions

In conclusion, understanding the complex interactions between heart failure and COVID-19 is essential for optimizing patient care. Early detection and effective treatment strategies are crucial in managing these patients.

Multidisciplinary approaches, including members of the heart failure team, can help patients with chronic heart failure better understand and treat diseases, including those who receive advanced treatments during this pandemic. It is still unclear whether SARS-CoV-2 infection increased the risk of venous thromboembolism or bleeding more than respiratory infections from other diseases, such as influenza, and whether the period of thromboprophylaxis after COVID-19 should be extended. In this context, future clinical trials will be useful.

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## 8. OŚWIADCZENIA WSPÓŁAUTORÓW PUBLIKACJI

**Prof. dr hab. n. med. Maciej Banach**

Kierownik Zakładu Kardiologii Prewencyjnej i Lipidologii

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Klinika Kardiologii i Wad Wrodzonych Dorosłych

Instytut Centrum Zdrowia Matki Polki w Łodzi

Łódź, 10.06.2024

OŚWIADCZENIE

Jako równorzędny autor publikacji:

1) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Maciejewski M, Bielecka-Dabrowa A.
***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction.***
Biomedicines. 2022 Dec 15;10(12):3257. doi: 10.3390/biomedicines10123257.

2) Gryglewska-Wawrzak K, Cienkowski K, Cienkowska A, Banach M, Bielecka-Dabrowa A.
***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19.***
J Cardiovasc Dev Dis. 2023 Jun 3;10(6):245. doi: 10.3390/jcdd10060245.

3) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bytyçi I, Bielecka-Dabrowa A.
***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction.***
J Clin Med. 2023 Jun 20;12(12):4160. doi: 10.3390/jcm12124160.

4) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bielecka-Dabrowa A.
***Predictors of Long-COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery.***
J Clin Med. 2023 Dec 14;12(24):7689. doi: 10.3390/jcm12247689.

oświadczam, iż w wyżej wymienionych pracach mój wkład w powstanie publikacji polegał na:

PUBLIKACJA 1

- krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 2

- krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

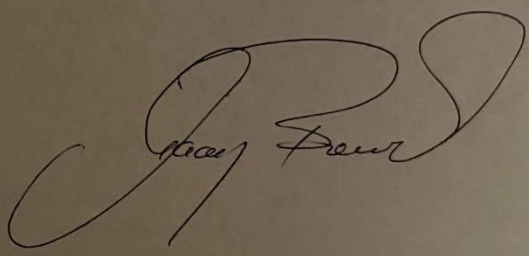
PUBLIKACJA 3

- krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 4

- krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w prac przedłożonych przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.



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OŚWIADCZENIE

Jako równorzędny autor publikacji:

1) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Maciejewski M, Bielecka-Dabrowa A.
***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction.***
Biomedicines. 2022 Dec 15;10(12):3257. doi: 10.3390/biomedicines10123257.

2) Gryglewska-Wawrzak K, Cienkowski K, Cienkowska A, Banach M, Bielecka-Dabrowa A.
***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19.***
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J Clin Med. 2023 Dec 14;12(24):7689. doi: 10.3390/jcm12247689.

oświadczam, iż w wyżej wymienionych pracach mój wkład w powstanie publikacji polegał na:

PUBLIKACJA 1

- stworzeniu konceptu pracy, interpretacji wyników, krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 2

- stworzeniu konceptu pracy, krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,

- mój udział w realizacji pracy szacuję na 15%.

PUBLIKACJA 3

- stworzeniu konceptu pracy, interpretacji wyników, krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 4

- stworzeniu konceptu pracy, interpretacji wyników, krytycznej ocenie treści artykułu, zaakceptowaniu ostatecznej treści artykułu,
- mój udział w realizacji pracy szacuję na 15%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w prac przedłożonych przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.

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**CO-AUTHORS STATEMENT**
**specifying their contribution to the article or monograph**

I declare that my contribution in the following article:

Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bytyçi I, Bielecka-Dabrowa A. ***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction.***
J Clin Med. 2023 Jun 20;12(12):4160. doi: 10.3390/jcm12124160.

is characterized in the table below:

| Author | Author Contributions % | Description of the contribution |
|---|---|---|
| Ibadete Bytyçi MD PhD FESC | 10% | substantive supervision and final review of the manuscript |

I hereby consent to the use of the aforementioned work submitted by Katarzyna Gryglewska-Wawrzak as part of the series of publications for her doctoral dissertation.

.....
*(signature of the co-author)*

**Alicja Cienkowska**

Studenckie Koło Naukowe

Uniwersytet Łódzki

Łódź, 29.05.2024

OŚWIADCZENIE

Jako równorzędny autor publikacji:

1) Gryglewska-Wawrzak K, Cienkowski K, Cienkowska A, Banach M, Bielecka-Dabrowa A.
***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19.***
J Cardiovasc Dev Dis. 2023 Jun 3;10(6):245. doi: 10.3390/jcdd10060245.

oświadczam, iż w wyżej wymienionej pracy mój wkład w powstanie publikacji polegał na wykonaniu rycin i krytycznej ocenie treści artykułu. Mój udział w realizacji pracy szacuję na 5%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy przedłożonej przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.

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Łódź, 29.05.2024

OŚWIADCZENIE

Jako równorzędny autor publikacji:

1) Gryglewska-Wawrzak K, Cienkowski K, Cienkowska A, Banach M, Bielecka-Dabrowa A.
***The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19.***
J Cardiovasc Dev Dis. 2023 Jun 3;10(6):245. doi: 10.3390/jcdd10060245.

oświadczam, iż w wyżej wymienionej pracy mój wkład w powstanie publikacji polegał na krytycznej ocenie treści artykułu. Mój udział w realizacji pracy szacuję na 10%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy przedłożonej przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.

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Instytut Centrum Zdrowia Matki Polki w Łodzi

Łódź, 28.05.2024

OŚWIADCZENIE

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1) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Maciejewski M, Bielecka-Dabrowa A.
***Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction.***
Biomedicines. 2022 Dec 15;10(12):3257. doi: 10.3390/biomedicines10123257

oświadczam, iż w wyżej wymienionej pracy mój wkład w powstanie publikacji polegał na krytycznej ocenie treści artykułu i zaakceptowaniu ostatecznej treści artykułu. Mój udział w realizacji pracy szacuję na 10%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy przedłożonej przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.

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Uniwersytet Medyczny w Łodzi

Łódź, 29.05.2024

OŚWIADCZENIE

Jako równorzędny autor publikacji:

1) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Maciejewski M, Bielecka-Dabrowa A.
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Biomedicines. 2022 Dec 15;10(12):3257. doi: 10.3390/biomedicines10123257.

2) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bytyçi I, Bielecka-Dabrowa A.
***Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction.***
J Clin Med. 2023 Jun 20;12(12):4160. doi: 10.3390/jcm12124160.

3) Gryglewska-Wawrzak K, Sakowicz A, Banach M, Bielecka-Dabrowa A.
***Predictors of Long-COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery.***
J Clin Med. 2023 Dec 14;12(24):7689. doi: 10.3390/jcm12247689.

oświadczam, iż w wyżej wymienionych pracach mój wkład w powstanie publikacji polegał na:

PUBLIKACJA 1

- wykonaniu analiz, obliczeniu statystycznym,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 2

- wykonaniu analiz, obliczeniu statystycznym,
- mój udział w realizacji pracy szacuję na 10%.

PUBLIKACJA 3

- wykonaniu analiz, obliczeniu statystycznym,
- mój udział w realizacji pracy szacuję na 15%.

Jednocześnie wyrażam zgodę na wykorzystanie w/w prac przedłożonych przez lek. Katarzynę Gryglewską-Wawrzak, jako części cyklu publikacji do przeprowadzenia przewodu doktorskiego.

Sakowicz Agata

# 9. ZAŁĄCZNIKI

## 9.1. Opinia Komisji Bioetycznej

*Komisja Bioetyczna*
*przy Instytucie Centrum Zdrowia Matki Polki*
93-338 Łódź, Rzgowska 281/289 tel. (42) 271 15 97
e-mail pnserca@iczmp.edu.pl

Łódź, dnia 22 grudnia 2020 r.

Dr hab. n. med. Agata Bielecka-Dąbrowa, prof. instytutu
Klinika Kardiologii i Wad Wrodzonych Dorosłych
Instytutu Centrum Zdrowia Matki Polki w Łodzi

Komisja Bioetyczna przy Instytucie Centrum Zdrowia Matki Polki działając zgodnie z zasadami Dobrej Praktyki Klinicznej na posiedzeniu w dniu 22 grudnia 2020 r. rozpatrywała wniosek dotyczący pracy:

**„Powikłania i wpływ COVID 19 na funkcję mięśnia sercowego i wydolność wysiłkową."**

Zespół badaczy:

1. Dr n. med. Marek Maciejewski
2. Prof. dr hab. n. med. Maciej Banach
3. Lek. Katarzyna Gryglewska
4. Prof. nadzw. Dr hab. n. med. Agata Bielecka-Dąbrowa

**Opinia Nr 75/2020**

Komisja Bioetyczna przy Instytucie Centrum Zdrowia Matki Polki zapoznała się z ww projektem eksperymentu medycznego, przeanalizowała wniosek, wysłuchała opinii recenzenta o przedstawionym projekcie i wyniku przeprowadzonej dyskusji oraz tajnego głosowania, po rozważeniu kryteriów etycznych oraz celowości i wykonalności projektu pozytywnie zaopiniowała projekt eksperymentu medycznego.

Uchwałę podjęto jednogłośnie.
Uchwałę podjęto przy sprzeciwie .....

Przewodnicząca:

Dr hab. med. Iwona Maroszyńska, prof. instytutu .....

Zastępca Przewodniczącej:

Prof. dr hab. n. farm. Daria Orszulak-Michalak .....

Członkowie:

Mec. Michał Araszkiewicz .....

Prof. dr hab. n. med. Tadeusz Biegański .....

Dr n. med. Paweł Czekalski .....

Dr hab. n. med. Piotr Grzelak, prof. instytutu .....

Mgr Grażyna Korybut .....

Dr n. med. Michał Krekora .....

Prof. dr hab. med. Jacek Rysz .....

Dr n. filozofii Wojciech Sztombka .....

Ks. dr hab. Jan Wolski .....

Dr hab. n. med. Marek Zadrożny, prof. instytutu .....

Prof. dr hab. n. med. Krzysztof Zeman .....

## 9.2. Informacja dla pacjenta biorącego udział w badaniu

### Informacja dla pacjenta biorącego udział w badaniu

**Tytuł badania: Powikłania i wpływ COVID-19 na funkcję mięśnia sercowego i wydolność wysiłkową**

COVID-19 to choroba wywołana przez wirus SARS-CoV-2 (koronawirus ostrej niewydolności oddechowej 2). Została po raz pierwszy opisana w listopadzie 2019 w Chinach (miasto Wuhan w prowincji Hubei) i w krótkim czasie doprowadziła do serii zachorowań na całym świecie. 11 marca WHO uznała COVID-19 za pandemię. Wirus przenosi się między ludźmi przede wszystkim drogą wziewną, a także prawdopodobnie drogą powietrzną i kontaktową. Głównym czynnikiem ryzyka zakażenia jest bezpośredni kontakt z osobą zakażoną, a także przebywanie w zamkniętym pomieszczeniu z osobą zakażoną i kontakt z materiałem zakaźnym bez środków ochronnych. Okres wylęgania określono na przeciętnie 5 dni, a wydalanie wirusa jest największe najprawdopodobniej tuż przed wystąpieniem objawów klinicznych i w pierwszych dniach po nim. Spektrum przebiegu infekcji jest szerokie: od bezobjawowego zakażenia, poprzez zakażenie objawowe niepowikłane zapaleniem płuc (nieswoiste objawy – podwyższenie temperatury ciała, ból głowy, utrata węchu i smaku, kaszel, złe samopoczucie, ból mięśni, zapalenie spojówek, biegunka), zapalenie płuc aż do zespołu ostrej niewydolności oddechowej i wstrząsu septycznego. Kryteria rozpoznania opierają się przede wszystkim na wykryciu materiału genetycznego SARS-CoV-2, a także parametrach klinicznych i radiologicznych. Leczenie w dużej mierze jest objawowe, obecnie nie ma ustalonych schematów leczenia przyczynowego. Niezwykle ważną rolę pełni zapobieganie rozprzestrzeniania się wirusa w populacji (dystans społeczny, dezynfekcja, maseczki ochronne).

Koronawirus SARS-CoV-2 i wywoływana przez niego choroba w dalszym ciągu kryje przed sobą wiele tajemnic. Zespoły badaczy z całego świata próbują poznać odpowiedzi na wiele pytań. Jednym z nich jest zagadnienie dotyczące powikłań po infekcji SARS-CoV-2. Na podstawie obserwacji pacjentów, którzy przebyli zakażenie można zauważyć, że COVID-19 powoduje szereg powikłań narządowych.

Badania przeprowadzone w ramach tej pracy pozwolą ocenić wpływ COVID-19 na rozwój chorób serca. Dzięki zaobserwowanym zależnościom możliwe będzie wczesne rozpoczęcie odpowiedniego postępowania diagnostycznego, dobór spersonalizowanego leczenia oraz

opracowanie modelu opieki kardiologicznej osób po przebytym zakażeniu wirusem SARS-CoV-2, a co za tym idzie poprawy jakości i wydłużenia ich życia.

Państwa udział w badaniu będzie polegał na pobraniu od Państwa dodatkowej próbki krwi podczas standardowego pobierania krwi do badań, w której zostaną oznaczone parametry biochemiczne oraz stężenie wybranych biomarkerów. Pozostałe zaplanowane badania obejmują pełne badanie kliniczne, ocenę płuc za pomocą tomografii komputerowej (CT) lub zdjęcia rentgenowskiego (RTG), badanie elektrokardiograficzne (EKG), rozszerzone badanie echokardiograficzne z oceną mięśnia sercowego z zastosowaniem dopplera tkankowego oraz oceną odkształcenia mięśnia lewej komory przy użyciu techniki śledzenia markerów akustycznych, badanie spiroergometryczne. Wydolność fizyczna zostanie oceniona w czasie badania spiroergometrycznego w warunkach szpitalnych. Po roku od wypisu ze szpitala zostanie u Państwa przeprowadzona kontrola stanu zdrowia z wykonaniem badania echokardiograficznego i spiroergometrii.

Państwa udział w badaniu jest całkowicie dobrowolny i mają Państwo możliwość odmowy, bądź wycofania zgody na udział w badaniu, w każdej chwili bez podania powodu oraz bez jakichkolwiek konsekwencji, a diagnozowanie i leczenie będzie się odbywało w ten sam sposób. Pobranie dodatkowej próbki krwi nie jest związane z ryzykiem pogorszenia stanu zdrowia i w miarę możliwości technicznych pobranie odbędzie się podczas rutynowego pobrania krwi na badania diagnostyczne, zlecone przez lekarza prowadzącego. Państwa dane osobowe ani inne dane wrażliwe, w tym umożliwiające identyfikację, nie zostaną w żaden sposób opublikowane ani upublicznione, a Państwa dokumentacja pozostaje poufna na dotychczasowych zasadach. Państwa ochrona przed niekorzystnymi zdarzeniami podczas udziału w badaniu pozostaje niezmieniona.

Niniejsza informacja dla pacjenta biorącego udział w badaniu jest Państwa własnością i na każdym etapie badania mogą się Państwo skontaktować z lekarzami prowadzącymi badanie w celu zadania dodatkowych pytań. Jeżeli wyrazili Państwo zgodę na przekazanie informacji, uzyskanych podczas badania, o ile będą one miały znaczenie w Państwa diagnostyce i leczeniu, lekarze prowadzący badanie skontaktują się z Państwem telefonicznie, listownie lub elektronicznie w przyszłości i przekażą te informacje.

### 9.3. Formularz świadomej zgody pacjenta na udział w badaniu

**Dane pacjenta:**

| | | | |
|---|---|---|---|
| Imię<br>i nazwisko: | | PESEL: | |
| Adres: | | telefon: | |

## Deklaracja świadomej zgody na udział w badaniu naukowym

Wyrażam świadomą zgodę na pobranie ode mnie materiału biologicznego oraz wykonanie oznaczeń biomarkerów biochemicznych we krwi oraz zaplanowanych badań nieinwazyjnych, w związku z moim udziałem w badaniu naukowym dotyczącym poszerzenia wiedzy na temat wpływu COVID-19 na rozwój chorób serca. Oświadczam, że zostałem poinformowany/a przez lekarza prowadzącego badanie o istocie badania. Oświadczam, że wyrażam zgodę na przechowywanie pobranego ode mnie materiału biologicznego w trakcie trwania oraz po zakończeniu badania. Wyrażam zgodę na publikację wyników badań wykonanych na podstawie pobranego ode mnie materiału biologicznego w artykułach naukowych, rozdziałach w książkach itp. oraz ich prezentację na konferencjach krajowych i zagranicznych, bez podawania danych umożliwiających identyfikację osoby, od której materiał został pobrany. Wyrażam zgodę na przetwarzanie moich danych osobowych przez Klinikę Kardiologii i Wad Wrodzonych Dorosłych ICZMP w Łodzi w celu rejestracji wykonywanych badań, zgodnie z przepisami ustawy z dnia 29 sierpnia 1997 roku o ochronie danych osobowych (Dz. U. z 2002 r. Nr 101, poz. 926 z późniejszymi zmianami). Oświadczam, że zostałem poinformowany/a o przysługującym prawie wglądu oraz korekty danych osobowych. Oświadczam, że zostałem poinformowany/a o możliwości wycofania swojej zgody na udział w badaniu na każdym etapie jego trwania. Oświadczam, że wyrażam zgodę na kontakt osób prowadzących badanie ze mną, zarówno w trakcie jego trwania, jaki i po jego zakończeniu.

Oświadczam, że **wyrażam / nie wyrażam** zgody na przekazanie mi informacji wynikających z wykonanych badań, jeżeli wyniki te mogą mieć znaczenie dla mojego zdrowia, leczenia bądź rokowania lub dla zdrowia, leczenia bądź rokowania u moich krewnych.

| | | |
|---|---|---|
| Miejscowość, data | Popis **lekarza** udzielającego informacji<br>i odbierającego zgodę | Podpis **pacjenta** biorącego udział w badaniu naukowym |

# 10. DOROBEK NAUKOWY

Dział Informacji Naukowej
Instytut Centrum Zdrowia Matki Polki
w Łodzi

## Lek. Katarzyna Gryglewska-Wawrzak

**Wszczęcie przewodu doktorskiego - wykaz publikacji wraz z punktacją (IF + MNiSW)**

| Lp. | Autorzy | Tytuł | Źródło | IF | Punktacja MEiN |
|---|---|---|---|---|---|
| 1. | **Gryglewska-Wawrzak Katarzyna,** Sakowicz Agata, Banach Maciej, Bytyci Ibadete, Bielecka-Dąbrowa Agata. | *Diagnostic Usefulness of Spiroergometry and Risk Factors of Long COVID in Patients with Normal Left Ventricular Ejection Fraction* | J Clin Med 2023 : 12, 12, 4160 | 3.000 | 140 |
| 2. | **Gryglewska-Wawrzak Katarzyna,** Sakowicz Agata, Banach Maciej, Bielecka-Dąbrowa Agata. | *Predictors of Long-COVID and Chronic Impairment of Exercise Tolerance in Spiroergometry in Patients after 15 Months of COVID-19 Recovery* | J Clin Med. 2023 : 12, 24, 7689 | 3.000 | 140 |
| 3. | **Gryglewska-Wawrzak Katarzyna,** Cienkowski Krzysztof, Cienkowska Alicja, Banach Maciej, Bielecka-Dąbrowa Agata. | *The Role of Multidisciplinary Approaches in the Treatment of Patients with Heart Failure and Coagulopathy of COVID-19* | J Cardiovasc Dev Dis 2023 : 10, 6, 245 | 2.400 | 20 |
| 4. | **Gryglewska-Wawrzak Katarzyna,** Sakowicz Agata, Banach Maciej, Maciejewski Marek, Bielecka-Dąbrowa Agata | *Factors of Persistent Limited Exercise Tolerance in Patients after COVID-19 with Normal Left Ventricular Ejection Fraction* | Biomedicines 2022 : 10, 12, 3257 | 4.700 | 100 |
| 5. | Bielecka-Dąbrowa Agata, **Gryglewska Katarzyna,** Sakowicz Agata, Rybak Marek, Janikowski Kamil, Banach Maciej. | *Obesity and Body Mass Components Influence Exercise Tolerance and the Course of Hypertension in Perimenopausal Women* | J Cardiovasc Dev Dis 2022 : 9, 8, 238 | 2.400 | 20 |
| 6. | Bielecka-Dąbrowa Agata, **Gryglewska Katarzyna,** Sakowicz Agata, von Haehling Stephan, Janikowski Kamil, Maciejewski Marek, Banach Maciej. | *Factors and Prognostic Significance of Impaired Exercise Tolerance in Women over 40 with Arterial Hypertension* | J Pers Med 2021 : 11, 8, 759 | 3.508 | 70 |

Punktacja zgodna z rokiem wydania publikacji.

ST. INSPEKTOR
DS. BIBLIOTEKOZNAWSTWA
Ewa Stawiak vel Konieczna

29.08.2024 r.
data i podpis osoby sporządzającej punktację

## 11. BIBLIOGRAFIA


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## 12. SPIS TABEL I RYCIN