ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of Autonomic Dysfunction Following COVID-19: the Role of Heart Rate Recovery Indices

COVID-19 Sonrası Otonomik Disfonksiyonun Araştırılması: Kalp Hızı İyileşmesi Parametrelerinin Rolü

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ABSTRACT

Aim: *COVID-19, caused by SARS-CoV-2, has been linked to long-term complications known as "long COVID," including autonomic dysfunction. Heart rate recovery (HRR) following exercise is a widely used marker for assessing autonomic function. This study evaluated HRR in Long-Term COVID patients and its association with inflammatory markers.*

Materials and Methods: *This retrospective study included 152 participants: 76 Long-Covid patients and 76 controls. Heart rate recovery was measured at 1, 2, 3, 4, and 5 minutes post-exercise using the Bruce protocol. Baseline demographic data and inflammatory markers, including CRP, D-dimer, and ferritin, were collected. Correlation analysis was performed between HRR and these markers.*

Results: *Long-Covid patients had significantly elevated levels of CRP (14.6±2.3 mg/L vs. 3.3±2.5 mg/L), D-dimer (128.2±42.1 µg/ml vs. 21.1±9.7 µg/ml), and ferritin (277.5±146.8 ng/ml vs. 112.3±78.2 ng/ml) compared to controls (p <0.001). HRR_1 and HRR_2 were significantly reduced in post-COVID patients (22.4±7.4 vs. 29.0±8.0; 31.5±17.4 vs. 40.2±10.9; p <0.001). Heart rate recovery at 3, 4, and 5 minutes was also markedly lower. A moderate negative correlation was found between HRR_2 and CRP (rs=-0.537), D-dimer (rs=-0.459), and ferritin (rs=-0.461) (p <0.001).*

Conclusion: *Long-Covid patients exhibited impaired HRR, indicating autonomic dysfunction, which correlated with elevated inflammatory markers. These findings highlight the importance of HRR as a marker for autonomic imbalance in Long-Covid, suggesting a need for further investigation into therapeutic strategies for autonomic dysfunction.*

Key words: *long COVID; heart rate recovery (HRR); autonomic dysfunction; inflammatory markers*

ÖZET

Amaç: *SARS-CoV-2'nin neden olduğu COVID-19,"Geç-Covid" olarak bilinen ve otonomik disfonksiyon da dâhil olmak üzere uzun vadede çeşitli komplikasyonlarla ilişkilendirilmiştir. Egzersiz sonrası kalp hızı iyileşmesi (HRR), otonom fonksiyonun değerlendirilmesinde yaygın olarak kullanılan bir göstergedir. Bu çalışma, Geç-Covid hastalarında HRR'yi ve bu iyileşmenin enflamatuvar belirteçlerle olan ilişkisini değerlendirmeyi amaçlamaktadır.*

Materyal ve Metod: *Bu retrospektif çalışmaya 76 Geç-Covid hastası ve 76 kontrol olmak üzere toplam 152 katılımcı dâhil edilmiştir. HRR, Bruce protokolü kullanılarak egzersiz sonrası bir, iki, üç, dört ve beşinci dakikalarda ölçülmüştür. Katılımcıların demografik verileri ve CRP, D-dimer ve ferritin gibi enflamatuvar belirteçler toplanmıştır. Kalp hızı iyileşmesi ile bu belirteçler arasında korelasyon analizi yapılmıştır.*

Bulgular: *Geç-Covid hastalarında CRP (14,6±2,3 mg/L vs. 3,3±2,5 mg/L), D-dimer (128,2±42,1 µg/ml vs. 21,1±9,7 µg/ml) ve ferritin (277,5±146,8 ng/ml vs. 112,3±78,2 ng/ml) seviyeleri kontrol grubuna kıyasla anlamlı derecede yüksekti (p <0,001). Geç-Covid hastalarında HRR_1 ve HRR_2 değerleri anlamlı şekilde düşüktü (22,4±7,4 vs. 29,0±8,0; 31,5±17,4 vs. 40,2±10,9; p <0,001). Kalp hızı iyileşmesi üç, dört ve beşinci dakikalarda da belirgin şekilde düşüktü. HRR_2 ile CRP (rs=-0,537), D-dimer (rs=-0,459) ve ferritin (rs=-0,461) arasında orta düzeyde negatif korelasyon bulundu (p <0,001).*

Sonuç: *Geç-Covid hastalarında otonom disfonksiyonu gösteren bozulmuş HRR gözlemlendi ve bu, yüksek enflamatuvar belirteçlerle ilişkiliydi. Bu bulgular, HRR'nin Geç-Covid'de otonom dengesizlik için bir belirteç olarak önemini vurgulamakta olup, otonom disfonksiyon için terapötik stratejilerin daha fazla araştırılmasının gerekliliğini ortaya koymaktadır.*

Anahtar kelimeler: *geç-covid; kalp hızı iyileşmesi (HRR); otonom disfonksiyon; enflamatuvar belirteçler*

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Introduction

The novel coronavirus disease (COVID-19), caused by the new type of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in Wuhan-China, and was declared a global pandemic by the World Health Organization on March 11, 2020. Since then, COVID-19 has led to significant morbidity and mortality worldwide[1]. Clinical manifestations during the acute phase of the infection vary widely, from mild upper respiratory symptoms to severe viral pneumonia that may result in multi-organ failure[2]. In a subset of patients who survive the acute phase, various symptoms persist or reemerge over an extended period. Symptoms that cannot be attributed to any other cause within the 4–12 weeks following COVID-19 infection are referred to as *"post-acute," "new,"* or *"ongoing"* COVID-19, while those lasting beyond 12 weeks are termed *"chronic," "long,"* or *"post-COVID"*[3]. Long COVID patients often report a range of dysautonomic symptoms, including palpitations, fatigue, and dizziness, but the exact mechanisms underlying these symptoms remain unclear[4]. Despite this uncertainty, the incidence of Long-Covid continues to rise, with profound impacts on both individual health and socioeconomic costs[5].

Heart rate recovery (HRR) following exercise, defined as the difference between the peak heart rate (HR) and the HR at various intervals during recovery, is a widely recognized marker of autonomic function[6,7]. Since dysautonomia is thought to play a role in Long-Covid, HRR could serve as a valuable marker for autonomic dysfunction in these patients[3,8]. Given that autonomic dysfunction is linked to adverse cardiovascular outcomes, assessing HRR in Long-Covid patients could provide valuable insights into their prolonged symptoms and potential cardiovascular risks[9,10].

Nevertheless, the available data on dysautonomia is limited, and no previous study has focused on HRR in the Long-Term COVID-19 population. This study aims to fill this gap by evaluating HRR in Long-Term COVID-19 patients, providing new insights into the autonomic dysregulation that may contribute to persistent symptoms. Understanding these mechanisms is essential for improving patient care and developing targeted rehabilitation strategies to address the long-term cardiovascular risks posed by COVID-19.

Material and Methods

Study Population

This retrospective study included patients diagnosed with COVID-19 via Polymerase Chain Reaction (PCR) testing between November 1, 2020, and January 1, 2021. All were treated on an outpatient basis without hospitalization and presented to the cardiology clinic at least 12 weeks after their positive test, following an asymptomatic period. These patients underwent exercise tests after reporting symptoms such as exertional dyspnea, palpitations, and/or atypical chest pain.

The control group consisted of individuals who underwent exercise testing before the pandemic (before December 2019) to exclude the possibility of asymptomatic or undiagnosed COVID-19 infection.

Exclusion criteria included patients with overt cardiovascular disease (e.g., coronary artery disease, arrhythmia, hypertension, left ventricular hypertrophy, or moderate to severe valvular heart disease), severe renal insufficiency (eGFR <50 ml/dak/1.73 m^2), morbid obesity, diabetes mellitus or obstructive sleep apnea. Patients who had experienced severe COVID-19 infections requiring intensive care or high-flow oxygen therapy or who were taking medications known to affect autonomic nervous system function (e.g., beta-blockers, inhaled beta-mimetics, atropine, glycosides, selective serotonin reuptake inhibitors, angiotensin-converting enzyme inhibitors), were also excluded. In addition, the study did not include patients who did not reach at least 85% of their age– and gender-predicted maximum heart rate during the exercise test.

The study included 152 participants who met the inclusion criteria and divided them into the 'COVID-19 (+) Group' and the age– and gender-matched 'Control Group'. Demographic data and biochemical, hematological, and inflammatory parameters were obtained from local databases. Figure 1 presents a study flowchart.

The study protocol adhered to the ethical principles outlined in the 1975 Declaration of Helsinki, and ethical approval was obtained from the local ethics committee.

Assessment of Heart Rate Recovery

All participants underwent an exercise stress test based on the Bruce protocol. The test was terminated once participants reached at least 85% of the age- and

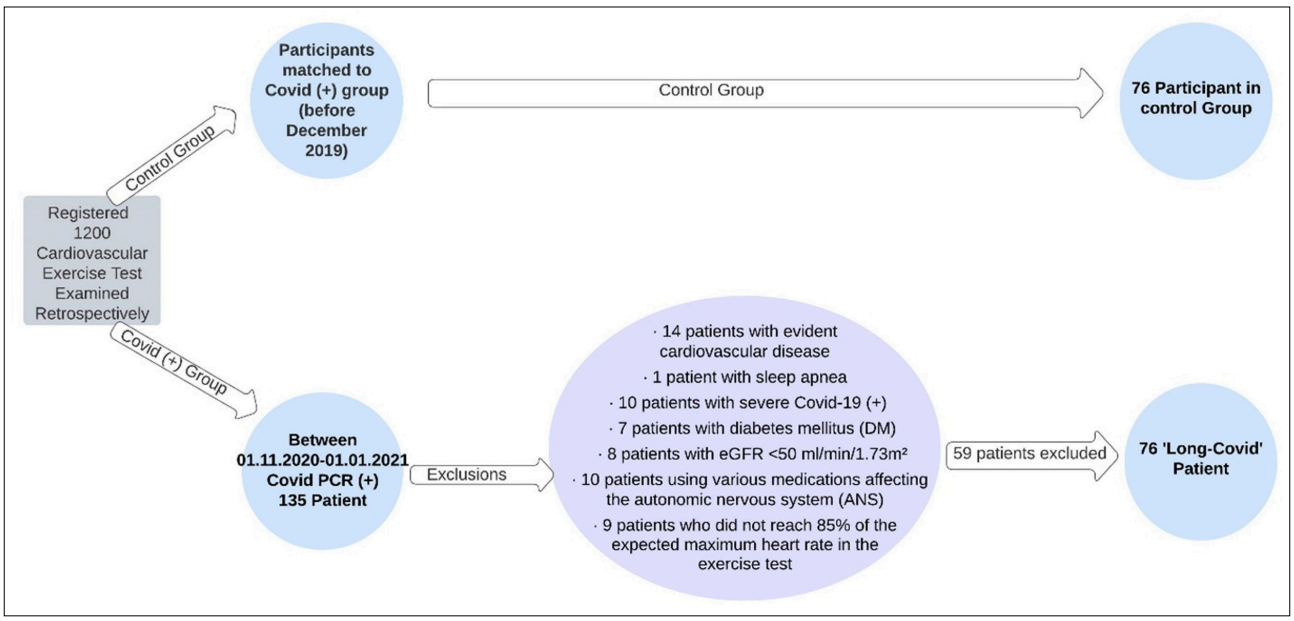

Figure 1. *Flowchart of the study population.*

gender-predicted maximum heart rate. After reaching peak exercise, participants immediately dismounted the treadmill and rested supine.

Heart rate measurements were taken at baseline, peak exercise, and recovery periods at 1, 2, 3, 4, and 5 minutes of the post-exercise period. Baseline (resting), peak exercise, and post-exercise blood pressure values were also recorded.

Definitions

COVID-19 Severity:

Mild COVID-19: Defined according to the World Health Organization (WHO) Guidelines as patients who were followed up on an outpatient basis, did not require hospitalization, and exhibited symptoms such as fever, muscle/joint pain, cough, or sore throat, without respiratory distress (respiratory rate <24/min, oxygen saturation on room air [SpO2] >93%)[11].

Long Covid: Signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). In this document, we used '***Long-Covid***' as signs and symptoms continue beyond the acute phase of COVID-19, in line with the definition by NICE and the NIH (who refer to it as post-Acute Sequelae of SARS-CoV-2 infection or PASC)[3,12].

HRR: HRR was defined as the peak heart rate minus heart rate at each recovery period (HR_{1-5}) after exercise[6].

HRR_1: Peak HR – Maximal HR at 1st minute of the recovery period.

HRR_2: Peak HR – Maximal HR at 2nd minute of the recovery period.

HRR_5: Peak HR – Maximal HR at the 5th minute of the recovery period.

Proportions of Heart Rate Recovery (PHRR): (HRR_2/ Resting pulse rate) × 100[13]

Systolic Blood Pressure (SBP) Change: SBP rise=Peak SBP – baseline (standing) SBP

Diastolic Blood Pressure Change: DBP rise=Peak DBP – baseline (standing) DBP

Exaggerated Blood Pressure response: The exaggerated BP response is peak exercise SBP ≥210 mmHg[14].

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) program version 22.0 for Windows (IBM Inc., Chicago, IL, USA) was used for all statistical analyses. The Kolmogorov-Smirnov test was performed to assess the normality of the distribution. Normally distributed quantitative variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Differences between groups were evaluated

Table 1. *Baseline characteristics and laboratory findings of the study population*

Parameters	COVID-19 Patients (n=76)	Control Group (n=76)	p value
Age, years	41.3±12.9	42.1±11.7	0.170
Male, n	44	37	0.255
HT, n	18	22	0.361
DM, n	9	12	0.221
Smoking, n	14	12	0.330
BMI, kg/m^2	25.2±1.7	24.9±1.7	0.403
WBC, 10^3 µL	7.9±4.3	7.0±3.9	0.069
Neutrophil, 10^3 µL	4.4±2.3	4.0±1.2	0.072
Hemoglobin, g/dL	13.6±0.8	13.7±0.6	0.195
Creatinin, mg/dl	0.9±0.09	1±0.15	0.392
Sodium, mEq/L	137±1.8	135.9±2	0.161
Potassium, mmol/L	4.4±0.3	4.2±0.3	0.406
ALT, IU/L	27.9±8.6	26.7±9.7	0.212
AST, IU/L	29.5±8.4	28.2±15	0.302
Total cholesterol, mg/dl	181±36	183±35.6	0.385
Triglyceride, mg/dl	139±36.8	134.6±36.1	0.081
HDL-C, mg/dl	36.1±8.9	37.1±7.6	0.182
LDL-C, mg/dl	118.7±26.1	117.1±27.21	0.291
Ferritin, ng/ml	277.5±146.8	112.3±78.2	<0.001
D-dimer, µg/ml	128.2±42.1	21.1±9.7	<0.001
CRP, mg/L	14.6±2.3	3.3±2.5	<0.001

Data are given as mean ± SD or n (%).
COVID-19:coronavirus disease 2019; DM: diabetes mellitus; HT: hypertension; BMI: body mass index; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; CRP: C-reactive protein.

using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using Chi-square tests. Spearman's correlation analysis examined the relationship between CRP, D-dimer, ferritin, and HRR_2. The strength of the correlations was interpreted as follows: 0–0.25 (weak), 0.26–0.50 (moderate), 0.51–0.75 (strong), and 0.76–1.00 (very strong). Statistical significance was defined as a p-value of <0.05.

Results

Table 1 summarizes the study groups' baseline clinical characteristics and laboratory parameters. The mean age of the participants was 41.6±11.9 years, and 53.3% were male. No significant differences regarding baseline demographic characteristics were observed between the COVID-19 and the control groups.

In the laboratory findings, the COVID-19 group exhibited significantly higher levels of D-dimer (128.2±42.1 µg/ml vs. 21.1±9.7 µg/ml; p <0.001), ferritin (277.5±146.8 ng/ml vs. 112.3±78.2 ng/ml; p <0.001), and C-reactive protein (CRP) (14.6±2.3 mg/L vs. 3.3±2.5 mg/L; p <0.001) compared to the control group. There were no significant differences between the groups in other laboratory parameters (p>0.05).

Table 2 presents the results of the exercise stress test and echocardiography. No significant differences were found between the groups in echocardiographic findings (p>0.05). Similarly, baseline and maximal heart rates, systolic and diastolic blood pressures, exercise duration, and metabolic equivalents achieved during the exercise stress test were comparable between the groups.

However, HRR indices in the COVID-19 group were significantly lower than those in the control group. The first-minute (HRR_1) and second-minute (HRR_2) HRR were markedly reduced in the COVID-19 group compared to the control group (22.4±7.4 vs. 29.0±8.0; p <0.001, and 31.5±17.4 vs. 40.2±10.9; p <0.001, respectively). Similarly, HRR indices at the third, fourth, and fifth minutes of the recovery period were significantly lower in the COVID-19 group (p <0.001 for all comparisons) (Figure 2).

Table 2. *Comparison of variables from echocardiography and exercise stress tests of COVID-19*

Coronavirus disease 2019 patients and controls			
Parameters	COVID-19 Patients (n=76)	Control Group (n=76)	p value
Echocardiographic findings			
LVEF (%)	65.3±6.7	64.9±6.5	0.790
LVEDD, mm	47.7±5.0	48.0±4.3	0.710
LVESD, mm	30.4±4.5	30.9±3.6	0.522
IVSD, mm	9.1±1.2	9.2±1.3	0.661
LVPWD, mm	8.4±1.3	8.3±1.0	0.436
PASP, mm Hg	26.3±5.1	25.3±5.6	0.372
Left atrial size, mm	31.2±3.8	30.4±4.0	0.350
Exercise stress test findings			
Exercise time, min	8.7±2.7	9.1±2.1	0.112
Baseline heart rate, beats/min	81±14.4	79.8±13.9	0.201
Maximal heart rate, beats/min	169.7±17.9	171.4±12.0	0.083
Maximal, METS	10.2±2.9	10.9±2.5	0.102
Baseline systolic BP, mm Hg	127.2±17.8	123.5±15.5	0.128
Baseline diastolic BP, mm Hg	78.3±10.3	76.6±11.5	0.142
Peak systolic BP, mm Hg	167.4 ±29.8	170.3±23.1	0.104
Peak diastolic BP, mm Hg	74.4±13.1	75.4±11.3	0.268
HRR_1	22.4±7.4	29.0±8.0	<0.001
HRR_2	31.5±17.4	40.2±10.9	<0.001
HRR_3	45.5±16.2	51.1±9.8	<0.001
HRR_4	53.2±13.4	59.3±11.7	<0.001
HRR_5	60±15.3	65.5±10.9	<0.001

Data are given as mean ± SD or n (%)
COVID-19: coronavirus disease 2019; Bpm: beats per minute; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVSD: interventricular septum diameter; LVPWD: left ventricular posterior wall diameter; LVEF: left ventricular ejection fraction; BP: blood pressure; METS: metabolic equivalents (1 MET=3.5 ml/kg/min of oxygen consumption); HRR: heart rate recovery.

A significant negative correlation was found between CRP levels (rs=-0.537, p <0.001), D-dimer levels (rs=-0.459, p <0.001), ferritin levels (rs=-0.461, p <0.001), and HRR_2 in patients with COVID-19.

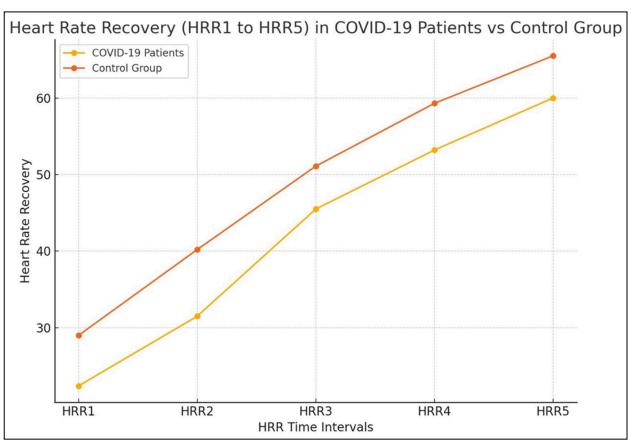

Figure 2. *Heart rate recovery indices difference between COVID-19 patients and the control group over the recovery intervals.*

Discussion

This study highlights the importance of assessing and monitoring autonomic nervous system-related symptoms as potential long-term complications of COVID-19. The main findings of the study are as follows: patients classified as 'Long-Covid,' who presented with various symptoms after the recovery from acute COVID-19, had significantly elevated levels of CRP, D-dimer, and ferritin. Furthermore, all heart rate recovery indices (HRR_{1-5}) measured during the exercise stress test were significantly lower in the COVID-19 group compared to the control group. Correlation analysis revealed a moderate negative correlation between HRR and infection-related markers (CRP, D-dimer, and ferritin).

The World Health Organization estimated in 2023 that millions of individuals could be affected by Long-Covid conditions and urged countries to take it seriously by investing in research, recovery, and

rehabilitation[15]. The typical Long-Covid syndrome includes symptoms like shortness of breath, palpitations, dizziness, and syncope, particularly when standing (orthostatic intolerance)[16]. Pathophysiologically, this is thought to result from either sympathetic activation due to a cytokine storm or direct viral damage leading to autonomic dysfunction[3,8,16]. In this context, dysautonomia is recognized as a component of Long-Covid syndrome, often manifesting as alterations in heart rate regulation. While many studies have evaluated early-phase orthostatic intolerance syndromes such as orthostatic hypotension (OH), vasovagal syncope (VVS), and postural orthostatic tachycardia syndrome (POTS), the long-term effects remain unclear[8].

Exercise testing is a valuable tool for evaluating individual exercise performance and understanding the various physiological processes that may become dysfunctional following COVID-19[16]. It can also evaluate autonomic nervous system function based on heart rate response to exercise. Several studies have explored this in COVID-19 patients. Clavario et al. reported that patients with more severe COVID-19 (defined by a percent-predicted peak oxygen uptake [%pVO_2] of <85%) exhibited lower peak heart rates at three months of post-infection period[17]. Jimeno-Almazán et al. demonstrated that even patients with mild COVID-19 could develop chronotropic incompetence and other autonomic disorders, which may contribute to long-term exercise intolerance after the resolution of acute infection[18]. Similarly, Ladlow et al. found significant evidence of dysautonomia in the same patient population using cardiopulmonary exercise testing and heart rate variability (HRV) assessments[19].

Asarcikli et al. evaluated HRV parameters using rhythm Holter monitoring in post-COVID patients during the 12–26 week period after infection. They found that HRV parameters were increased in COVID patients compared to controls, indicating heightened parasympathetic tone, although no significant changes were noted in the sympathetic system[2]. Another study by Yüksel et al. found that psoriasis patients had significantly reduced HRR_{1-5} parameters, demonstrating autonomic dysfunction in this patient group[20]. Huckstep et al. reported lower HRR_{1-2} in young adults born preterm, highlighting the potential long-term effects of early-life conditions on autonomic function[21]. Additionally, Dewar et al. showed that reduced HRR in patients with cardiovascular disease is associated with cardiovascular and all-cause mortality[22].

Recent studies have comprehensively evaluated patients who have recovered from COVID-19 based on their long-term symptomatic status. In a study by Karakayali et al., electrocardiographic parameters related to ventricular depolarization and repolarization were examined in symptomatic and asymptomatic patients post-COVID period[23]. The study revealed that fragmented QRS was significantly more prevalent in symptomatic individuals, suggesting its potential role as a predictor of cardiac symptoms such as palpitations and chest discomfort. A notable difference was observed in the Tpeak-Tend interval, which was significantly lower in symptomatic patients[23]. In another study by Karakayali et al., valuable insights into autonomic dysfunction in post-COVID patients were provided[24]. The study found no significant difference in autonomic function between symptomatic and asymptomatic individuals; however, symptomatic patients exhibited a higher burden of silent ischemia, characterized by increased ST depression and HRV measurements[24]. These findings indicate a complex relationship between cardiac symptoms and autonomic nervous system function in the post-COVID period and highlight the need for further research into the impact of COVID-19 on autonomic dysfunction.

In our study, long-term COVID patients exhibited significantly lower HRR_{1-5} than the control group. Furthermore, HRR_2 showed a significant negative correlation with disease markers such as CRP, D-dimer, and ferritin. These findings underscore the importance of dysautonomia, as indicated by impaired HRR, in the post-COVID period. Impaired HRR may serve as a marker of autonomic imbalance, which could contribute to the persistent symptoms experienced by long-term COVID-19 patients.

Limitations

This study has several limitations that should be considered when interpreting the results. First, its retrospective design may introduce selection bias, as it only includes patients who presented to the cardiology clinic with symptoms after their COVID-19 infection. The lack of longitudinal follow-up also limits the ability to determine the long-term effects of autonomic dysfunction in long-term COVID patients.

Second, the sample size was relatively small, with only 76 patients in the COVID-19 (+) group meeting the inclusion criteria, which may reduce the generalizability of the findings.

Finally, exercise stress testing to assess autonomic function might not capture all aspects of autonomic dysregulation, particularly in those with subtle or non-exercise-related dysfunctions. Further studies with larger, more diverse populations and extended follow-up periods are needed to validate these findings and explore the full spectrum of autonomic dysfunction in post-COVID patients.

Conclusion

This study highlights the significance of assessing and monitoring autonomic nervous system-related symptoms as potential long-term complications of COVID-19. The main findings indicate that patients categorized as 'Long-Covid' demonstrated significantly higher CRP, d-dimer, and ferritin levels. Furthermore, all HRR parameters (HHR_{1-5}) were notably lower in the Covid-19 (+) group. A moderate negative correlation was observed between HRR and disease-related parameters (CRP, d-dimer, and ferritin), suggesting a relationship between impaired autonomic function and inflammation markers in Long-Covid conditions. The findings of this study emphasize the importance of HRR as a marker of autonomic dysfunction in Long-Covid patients, highlighting the need for further research to explore the long-term impacts and develop appropriate therapeutic strategies.

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Disclosures

Conflict of interest: No financial or other relationship might be perceived as leading to a conflict of interest.

Informed Consent: Informed consent was obtained from all the participants included in the study.

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