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Autonomic dysfunction and metabolic disorders as the possible sequelae of COVID-19 infection

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Abstract. – OBJECTIVE: The Coronavirus disease 2019 (COVID-19) infection is associated with autonomic dysfunction. Data on the long-term relationship between COVID-19 infection, heart rate recovery (HRR), and exaggerated blood pressure response to exercise (EBPR) are very limited. In our study, we aimed at investigating the long-term association between COVID-19, HRR, EBPR, metabolic, and echocardiographic parameters.

PATIENTS AND METHODS: The study included 65 patients in the study group (33 female, median age 46) and 57 in the control group (30 female, 39 median age) between 1 April 2020 and 1 January 2021. Office blood pressure measurement, 24-hour ambulatory blood pressure monitoring, treadmill test, echocardiography, and metabolic parameters were evaluated.

RESULTS: The frequency of blunted HRR (25 subjects, 38.5%, $p < 0.001$) and EBPR (7 subjects, 10.8%, $p = 0.014$) were significantly higher in study group. The study group had higher levels of white blood cell ($p = 0.002$), neutrophil, c-reactive protein, and uric acid ($p < 0.001$). Diameters of left atrium, aortic root, and ascending aorta were significantly higher in study group ($p < 0.05$). Age adjusted multiple logistic regression analysis showed that neutrophil levels (odds ratio (OR), 9.21; 95% confidence interval (CI), 1.52-55.75, $p = 0.016$), glomerular filtration rate (OR, 1.34; 95% CI, 1.13-1.59, $p = 0.001$), basal heart rate (OR, 1.58; 95% CI, 1.17-2.12, $p = 0.003$), and mean heart rate (OR, 1.22; 95% CI, 1.03-1.45, $p = 0.0021$) were independently associated with COVID-19 infection.

CONCLUSIONS: The frequency of blunted HRR and EBPR, and uric acid levels were significantly higher in the study group compared to the control group, suggesting autonomic dysfunction as the possible sequelae of the COVID-19 infection and increased risk of cardiovascular events in the future.

Key Words:
COVID-19, Autonomic dysfunction, Heart rate recovery, HRR, Exaggerated blood pressure response to exercise, EBPR, Metabolic parameters.

Introduction

The Coronavirus disease 2019 (COVID-19) outbreak has affected over 450 million people worldwide, causing more than 6 million death since late 2019[1]. Although the respiratory system is mainly affected in the acute period, the cardiovascular system, gastrointestinal system, and central nervous system may also be affected. Symptoms can range from asymptomatic or mild upper respiratory tract infection to severe clinical conditions resulting in respiratory failure, multiorgan failure, and death[2].

It has been revealed that COVID-19 is closely associated with renin-angiotensin-aldosterone system (RAAS) imbalance, systemic inflammation, endothelial dysfunction, microvascular dysfunction, and coagulatory disorders in both acute phase and long term[3]. The autonomic nervous system has a key role in the regulation of whole-body homeostasis, including the immune system, cardiovascular system, hematological system, and microvascular function, and is of vital importance in terms of prognosis in COVID-19 infection[4]. It has been shown that the COVID-19 virus causes autonomic dysfunction through activation of the sympathetic nervous system and withdrawal in the parasympathetic nervous system during infection[5]. Therefore, evaluation of the cardiac autonomic function in patients with a history of COVID-19 infection can be very useful to identify the risk of developing adverse cardiovascular outcomes in the future[6].

Heart rate recovery (HRR) is used as a non-invasive and simple tool to evaluate cardiac autonomic activity in patients and healthy individuals and is a powerful index to predict mortality[7]. Many studies have shown that blunted HRR, defined as $\leq$ 12 bpm reduction in heart rate (HR) from peak exercise to 1 minute into recovery, is a strong predictor of overall mortality[8,9]. Exaggerated blood pressure response to exercise (EBPR)

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is another parameter known to be associated with increased sympathetic activity, impaired endothelial vasodilator function, and adverse cardiovascular outcomes[10].

The association between COVID-19 and autonomic dysfunction has recently become a very important research topic, but the mechanism is still not clarified. Moreover, HRR parameters and EBPR after COVID-19 infection have not been evaluated so far. In our study, we aimed at investigating autonomic dysfunction of the cardiovascular system using blunted HR and EBPR parameters in patients 1 year after the COVID-19 infection.

Patients and Methods

The study was approved by the local ethics committee of Kirikkale University in terms of compliance with the Helsinki principles (Date: 27.01.2022, Decision number: 2022.01.30), and informed written consent was obtained from all participants included in this single-center, case-control, and cross-sectional study. The study included 65 patients with a history of COVID-19 infection one year or more ago, and 57 healthy controls without a history of COVID-19 vaccine or COVID-19 infection between April 2020 and April 2021. Cases with diabetes mellitus, hypertension, severe liver or kidney disease, neurological disorder, moderate/severe valvular heart disease, arrhythmia, heart failure, obstructive sleep apnea, endocrine system disorder, pulmonary, malignant disease, obesity, autoimmune disease, or a history of multiorgan failure during the COVID-19 infection were excluded from the study. Both groups underwent a nasal and oropharyngeal swab to exclude a possible asymptomatic infection. The past medical history of the participants was recorded and a detailed physical examination was performed.

Blood Pressure Measurement and 24-Hour Ambulatory Blood Pressure Monitoring

Office blood pressure measurement was carried out by the same doctor for each patient by measuring 3 times with an interval of 5 minutes. Blood pressure (BP) measurements were performed by a Riester brand (Riester big ben round, Jungingen, Germany) mercury sphygmomanometer in a quiet environment and after resting for at least 5 minutes while sitting. The mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were recorded.

24-hour ambulatory blood pressure monitoring (ABPM) was performed on each participant's non-dominant arm by the Oscar 2 oscillometric 24-hour ABPM system (SunTech Medical Inc., Morrisville, NC, USA) on all individuals included in the study. The accuracy of the ABPM device was confirmed with a standard mercury sphygmomanometer. ABPM measurement started at 10:00 AM and ended at the same time the next day. In the printout of the records, the measurements between 08:00 AM and 10:00 PM were defined as daytime measurements, and those between 10:00 PM and 08:00 AM were defined as nighttime measurements. The device was set to measure at 20-minute intervals in the daytime and 40-minute intervals at nighttime. Study participants were instructed to continue their usual daily activities during the daytime and rest or sleep during the nighttime. 24-hour mean SBP and DBP levels, daytime mean SBP and DBP levels, nighttime mean SBP and DBP levels, and BP variability were calculated.

Treadmill Test

Participants in the study underwent a symptom-limited exercise test (Marquette Electronics, Milwaukee, WI, USA) according to the modified Bruce protocol[11]. During the procedure, a 12-lead electrocardiography recording was obtained and printed at a paper speed of 25 mm/s. During the test, SBP and DBP measurements were performed at 3-minute intervals in the non-dominant arm with an automatic device. The measurements of HR and BP were recorded at the end of each 3-min stage at peak exercise and at 1-min and 2-min intervals throughout recovery. The treadmill test was terminated when the participant had intolerable fatigue or more than 95% of the maximal HR (220 bpm) was reached, and the duration of the test was recorded. Peak exercise SBP $\geq$ 210 mmHg in men and $\geq$ 190 mmHg in women was defined as EBPR[12]. During the recovery phase, subjects continued walking at 1.5 mph for 1 minute, followed by 3 minutes of sitting and resting, with continuous monitoring of blood pressure, heart rate, and heart rhythm. Blunted HRR was defined as heart rate difference $\leq$ 12 bpm between peak HR and HR 1 minute after peak HR[13].

Echocardiographic Measurements

Standard 2-dimensional echocardiography was performed by the same physician on all subjects lying in the left lateral decubitus position with a Vivid 7 Doppler echocardiographic unit

(GE Vingmed Ultrasound, Horten, Norway) using a 3.5-MHz transducer. Echocardiographic measurements were made according to ACC and AHA standard protocols[14]. Two-dimensional and M-mode echocardiography were utilized to investigate ejection fraction (EF), left ventricular mass index (LVMI), the left atrium (LA) diameter, the diameter of the aortic root, and the ascending aortic diameter. Tissue doppler imaging techniques were used to assess the following: late diastolic myocardial velocity (Am), early diastolic myocardial velocity (Em), Em/Am ratio (Em/Am). Increased Am, decreased Em and Em/Am ratios implied a decreased ventricular diastolic function. For further analyses, the average value of the measurements obtained along with three consecutive cardiac cycles was used.

Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) program was used in the analysis of the variables. While the normal distribution of the data was evaluated with the Shapiro-Wilk and Shapiro-Francia test, the Levene's test was used to evaluate the homogeneity of variance. In the comparison of the quantitative data of two independent groups, Independent-Samples *t*-test with the Bootstrap results or the Mann-Whitney U test with Monte Carlo results were used. In the comparison of categorical variables, the Pearson Chi-Square test with the Monte Carlo Simulation technique was performed and column ratios were compared with each other using the Benjamini-Hochberg method. Odds ratio with 95% confidence intervals was used to determine how many times those who were exposed to a risk factor showed more effects than those who were not. Multiple logistic regression test (Backward Stepwise, Wald) was used to determine the cause-effect relationship between study groups and the explanatory variables. While quantitative variables were expressed as mean±standard deviation and median (percentile 25 – q1 / percentile 75 – q3), categorical variables were shown as numbers (%). The variables were analyzed at 95% confidence level, and a *p*-value lower than 0.05 was considered significant.

Results

The study included 65 patients in the study group (33 female, median age 46) and 57 healthy subjects (30 female, 39 median age). Basic demographic profile, clinical, and laboratory findings are presented in Table I. The median age of the study group was significantly higher than in the

Table I. Comparison of the demographic, clinical, and laboratory characteristics of the two groups.

	Total (n=122)	Control group (n=57)	Study group (n=65)	*p*
Gender (Female), n (%)	63 (51.6)	30 (52.6)	33 (50.8)	0.858[c]
Age, years	43.5 (39 / 48)	39 (36 / 44)	46 (43 / 49)	**<0.001**[u]
BMI, kg/m²	22.3 (21.5 / 23)	22.3 (21.6 / 22.9)	22.4 (21.4 / 23)	0.329[u]
Smoking, n (%)	46 (37.7)	15 (26.3)	31 (47.7)	**0.024**[c]
Symptoms				
Orthostatic headache, n (%)	12 (9.8)	1 (1.7)	12 (18.5)	**0.003**[c]
Vertigo, n (%)	11 (9)	1 (1.7)	11 (16.9)	**0.005**[c]
Palpitation, n (%)	40 (32.8)	3 (5.3)	40 (61.5)	**<0.001**[c]
Sweating, n (%)	22 (18)	2 (3.5)	22 (33.8)	**<0.001**[c]
Laboratory findings				
Hemoglobin, (g/dL)	14.6±1	14.6±0.9	14.7±1.1	0.573[t]
White blood cell, (10^{*9}/L)	6.9 (5.9 / 8)	6.8 (5.8 / 7.1)	7.5 (6 / 9)	**0.002**[u]
Neutrophil, (10^3/µL)	3.5 (3.1 / 4.5)	3.3 (3 / 3.4)	4.3 (3.5 / 5.8)	**<0.001**[u]
Lymphocytes, (10^3/µL)	2.6 (2.3 / 2.9)	2.7 (2.6 / 2.9)	2.3 (2 / 2.7)	**<0.001**[u]
Platelet, (10^{*9}/L)	284 (245 / 299)	290 (247 / 299)	282 (244 / 300)	0.453[u]
C-reactive protein, (mg/dL)	0.3 (0.2 / 0.9)	0.2 (0.1 / 0.3)	0.8 (0.3 / 1)	**<0.001**[u]
Glomerular filtration rate, (ml/dk/1.73 m²)	110.1 (103.5 / 119)	118 (113 / 123)	106 (97.8 / 110)	**<0.001**[u]
Uric acid, mg/dL	4.9 (4.1 / 5.7)	4.4 (4 / 4.9)	5.6 (4.5 / 6)	**<0.001**[u]

[t]Independent Samples *t*-test (Bootstrap), [u]Mann-Whitney U Test (Monte Carlo), [c]Pearson Chi-Square test (Monte Carlo). Shown as median (1st quartile/3rd quartile) for non-normally distributed data, mean±standard deviation for normal distribution, and n (%) for categorical data.

Table II. Parameters of treadmill test and 24-hour ambulatory blood pressure monitoring.

	Total (n=122)	Control group (n=57)	Study group (n=65)	*p*
Heart rate (Treadmill test), bpm				
Basal heart rate	88 (78 / 96)	79 (72 / 87)	94 (88 / 105)	**<0.001**[u]
Max heart rate	155 (145 / 163)	151 (144 / 160)	158 (150 / 164)	**0.026**[u]
HR at recovery 1st min	140.5±14.7	136.2±14.4	144.4±13.9	**0.003**[t]
HR at recovery 2nd min	131.3±14.3	127.2±14.7	134.9±12.9	**0.003**[t]
HR at recovery 3rd min	122.9±15	118.2±15.4	127±13.4	**0.002**[t]
Mean heart rate	106.5±13.7	102.2±10.9	110.3±14.9	**0.002**[t]
Office heart rate, bpm	81.5 (75 / 91)	78 (73 / 90)	85 (76 / 92)	**0.042**[u]
Blunted HR	27 (22.1)	2 (3.5)	25 (38.5)	**<0.001**[c]
Blood pressure (mmHg)				
Exercise SBP	145 (140 / 155)	140 (135 / 145)	155 (145 / 160)	<**0.001**[u]
Exercise DBP	90 (85 / 95)	90 (85 / 90)	95 (90 / 100)	<**0.001**[u]
EBPR, n (%)	7 (5.7)	0 (0)	7 (10.8)	**0.014**[f]
24-hour ambulatory blood pressure monitoring, mmHg				
SBP daytime	116 (110 / 125)	110 (105 / 117)	123 (115 / 130)	**<0.001**[u]
DBP daytime	75 (70 / 80)	72 (70 / 75)	78 (73 / 82)	**<0.001**[u]
SBP nighttime	103±12.5	96.6±8.8	108.6±12.7	**0.001**[t]
DBP night	63 (60 / 70)	60 (60 / 65)	65 (60 / 72)	**<0.001**[u]
MBP daytime	88 (83 / 95)	84 (80 / 89)	93 (87 / 98)	**<0.001**[u]
MBP night	75.5 (72 / 83)	73 (70 / 77)	82 (74 / 90)	**<0.001**[u]
Dipping, % (sistole)	12 (11 / 13)	11 (11 / 13)	12 (8 / 13)	0.480[u]
Dipping, % (diastole)	14 (12 / 16)	14 (12 / 15)	14 (9.3 / 16)	0.670[u]
Office SBP, mmHg	120 (110 / 128)	120 (110 / 130)	120 (110 / 125)	**0.015**[u]
Office DBP, mmHg	70 (65 / 80)	70 (65 / 80)	70 (65 / 76)	0.241[u]
Ejection fraction, %	64 (60 / 65)	65 (60 / 65)	62 (56 / 65)	**0.021**[u]
Left atrium diameter, mm	34 (32 / 35)	33 (32 / 35)	34 (33 / 36)	**0.023**[u]
Aortic root diameter, mm	32 (30 / 34)	31 (30 / 33)	33 (32 / 34)	**<0.001**[u]
Ascending aorta diameter, mm	31 (30 / 33)	30 (29 / 32)	32 (31 / 33)	**<0.001**[u]
LVH	3 (2.5)	0 (0)	3 (4.6)	0.247[c]

HR: Heart rate, EBPR: Exaggerated blood pressure response, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, LVH: Left ventricular hypertrophy.
[t]Independent Samples *t*-test (Bootstrap), [u]Mann-Whitney U test (Monte Carlo), [c]Pearson Chi-Square test (Monte Carlo), [f]Fisher Exact Test (Monte Carlo).
Shown as median (1st quartile/3rd quartile) for non-normally distributed data, mean±standard deviation for normal distribution, and n (%) for categorical data.

control group ($p < 0.001$). Both groups were similar in terms of gender and BMI ($p = 0.858$; $p = 0.329$). The frequency of smoking habits was significantly higher in the study group ($p = 0.024$). Palpitation was the most common symptom (61.5%) and its frequency was significantly higher in the study group ($p < 0.001$). The frequency of other symptoms such as orthostatic headache, vertigo, and sweating were also higher in study group ($p = 0.003$; $p = 0.005$; $p < 0.001$). In laboratory data, patients with COVID-19 history had higher white blood cell (WBC), neutrophil, c-reactive protein (CRP), uric acid ($p = 0.002$; $p < 0.001$) but lower lymphocyte levels and glomerular filtration rate (GFR) ($p < 0.001$).

Treadmill test, 24-hour ambulatory blood pressure monitoring, and echocardiography findings were presented in Table II. Heart rate (basal, maximum, and mean), SBP (daytime, nighttime, and during exercise), DBP (daytime, nighttime, and during exercise) and mean BP (daytime and nighttime) values were found to be significantly higher in the study group compared to healthy controls ($p < 0.005$). The frequency of blunted HRR (25 subjects, 38.5%) and EBPR (7 subjects, 10.8%) were also significantly higher in study group ($p < 0.001$; $p = 0.014$). A cut-off value of 91 bpm for basal HR was suggested to be used in the differentiation of COVID-19-related autonomic dysfunction with a sensitivity of 66.2% and a specificity of 96.5% (AUC = 0.863, $p < 0.001$), and 102 bpm for mean HR with a sensitivity of 72.3% and a specificity of 59.6% (AUC = 0.681, $p < 0.001$) (Figure 1).

As echocardiographic parameters, EF was lower ($p = 0.021$), but LA diameter, aortic root diameter, and ascending aorta diameter were mildly higher in

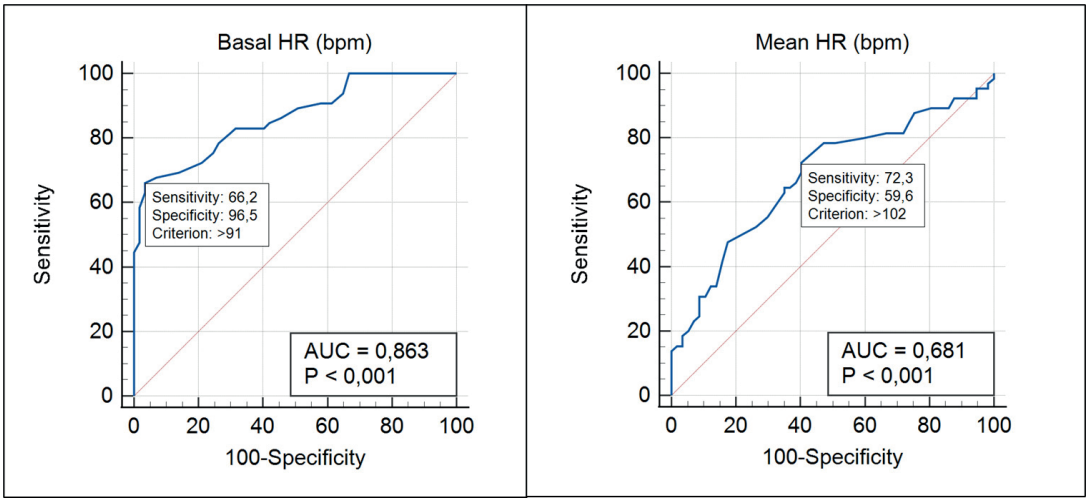

Figure 1. ROC curves for basal and mean heart rate.

the study group ($p < 0.005$). In terms of frequency of left ventricular hypertrophy (LVH), there was no significant difference between the two groups.

Age adjusted multiple logistic regression analysis showed that neutrophil levels [odds ratio (OR), 9.21; 95% confidence interval (CI), 1.52-55.75, $p = 0.016$], GFR (OR, 1.34; 95% CI, 1.13-1.59, $p = 0.001$), basal HR (OR, 1.58; 95% CI, 1.17-2.12, $p = 0.003$), and mean HR (OR, 1.22; 95% CI, 1.03-1.45, $p = 0.0021$) were independently associated with the COVID-19 infection (Table III).

Discussion

The major findings of this study are as follows: 1) COVID-19 infection was closely associated with blunted HR and EBPR, which are signs of the significantly impaired autonomic nervous system as long-term sequelae. 2) COVID-19 was closely associated with higher uric acid levels in the long term. 3) Even in mild COVID-19 infection, systemic inflammation may continue during the chronic period. These findings suggest a significant association between COVID-19, chronic inflammation, and autonomic dysfunction that may pose a risk of cardiovascular events in the future.

The autonomic nervous system plays a vital role in maintaining the balance of the body such as regulation of whole-body homeostasis, including the immune system, cardiovascular system, hematological system, and microvascular function[4]. Therefore, it is crucial to understand the effect of COVID-19 infection on the autonomic nervous system. COVID-19 adversely affects the autonomic nervous system in many ways. The virus

Table III. Risk factors associated with COVID-19 according to multiple logistic regression analysis.

	p-value	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Adjusted with Age				
Neutrophil (↑)	0.016	9.21	1.52	55.75
Glomerular filtration rate (↓)	0.001	1.34	1.13	1.59
Basal heart rate (↑)	0.003	1.58	1.17	2.12
Mean heart rate 1st min (↑)	0.021	1.22	1.03	1.45
Not Adjusted with Age				
Neutrophil (↑)	0.007	12.48	2.02	77.21
Glomerular filtration rate (↓)	<0.001	1.38	1.16	1.63
Basal heart rate (↑)	0.001	1.68	1.25	2.26
Mean heart rate 1st min (↑)	0.007	1.25	1.06	1.48

Multiple Logistic Regression (Method = Backward Stepwise - Wald); C.I.: Confidence interval.

causes the cytokine response storm by inducing sympathetic hyperactivation and parasympathetic withdrawal, which induces proinflammatory cytokine releases[15,16]. Antibodies against the virus may cause autonomic dysfunction, such as orthostatic hypotension and postural orthostatic tachycardia syndrome (POTS)[15]. The virus itself may also enter the central nervous system by invasion through the olfactory epithelium and involve the hypothalamus and brain stem, causing autonomic dysfunction[6,17]. Patients with diseases already characterized by increased sympathetic activity, such as hypertension, diabetes mellitus, and ischemic heart disease, are at higher risk of morbidity and mortality due to hypoxemia, systemic inflammation, and increased sympathetic activity during the COVID-19 infection[16,18]. Nam et al[19] observed that patients with hypertension had higher in-hospital mortality than those without hypertension. Similarly, Guan et al[20] observed that mortality and morbidity were higher in conditions such as hypertension, diabetes mellitus, coronary heart disease, and cerebrovascular disease.

The endothelial vasomotor function may also be affected due to autonomic nervous system dysfunction. This may lead to an increased frequency of thrombosis-related events, such as cerebrovascular events, acute coronary syndrome, deep vein thrombosis, and pulmonary embolism, in both acute and chronic periods, resulting in increased mortality and morbidity, even in healthy individuals[21-24]. Currently, there is also an opinion that COVID-19 may cause autonomic dysfunction, leading to systemic diseases such as diabetes mellitus and hypertension in healthy individuals in the future[25]. Along with many mechanisms, it is presented as the main hypothesis that the effect of significantly increased lactic acid production and impaired insulin secretion in the pancreas due to autonomic nervous system dysfunction may lead to diabetes mellitus[25]. Rubino et al[26] reported that even new-onset diabetes may be the first clinical presentation of COVID-19 patients. It has been revealed that other viruses can cause diabetes mellitus by different mechanisms. Yoon et al[27] reported that Coxsackievirus B4 virus caused lymphocyte infiltration and beta cell necrosis in the islets of Langerhans in the post-mortem examination of a patient who died due to diabetic ketoacidosis. In addition, Serfaty[28] suggested that human hepatitis C virus (HCV) may cause diabetes mellitus as a result of direct inhibition of the insulin signaling pathway by the HCV core protein in the liver, overproduction of tumor necrosis factor-alpha, oxidative stress, modulation of incretins, or pancreatic β-cell dysfunction. During COVID-19 infection, patients may present with neurological manifestations. Even cases of COVID-19 presenting with Guillain Barre syndrome as a result of autonomic nervous system involvement have been reported[29].

The relationship between COVID-19 and autonomic dysfunction has been the subject of many studies[4,6,7,30-36]. Most of these studies[4,6,30] investigated the relationship between heart rate variability (HRV) and the severity of the disease and metabolic parameters. However, we preferred to use HRR rather than HRV in our study. HRR, like HRV, is a non-invasive and simple test, reflecting the dynamic balance and coordinated interaction between parasympathetic reactivation and sympathetic withdrawal, and is a very useful test for predicting future cardiovascular events and all-cause mortality in both healthy and sick individuals[31]. The advantage of HRR over HRV is that the data for reduced HRR is obtained through treadmill tests and does not require 24-hour Holter monitoring or specialized baroreflex sensitivity testing[32]. Another advantage of HRR over HRV is that early recovery after exercise reflects parasympathetic reactivation, a key determinant of autonomic dysfunction, independent of age and exercise intensity[33]. In many important clinical studies conducted to date[7,31,34-36], the HRR has been used to evaluate autonomic dysfunction, future cardiovascular events, and all-cause mortality. Moreover, each 10 bpm decrease in HRR increased the risk by 13% and 9%, respectively. In a meta-analysis[37], blunted HRR was reported to be associated with an increased risk of diabetes mellitus, a major risk factor for cardiovascular events, in a dose-dependent manner. In another study including 2,740 healthy men, it was reported that delayed HRR was significantly associated with the risk of cardiometabolic syndrome in the future[38]. In the light of aforementioned studies, we evaluated the long-term effects of COVID-19 on the autonomic nervous system based on HRR in our study and found blunted HR in 38.5% of the patients in the study group. To the best of our knowledge, our study is the first study investigating the association between COVID-19-related-autonomic dysfunction and HRR.

EBPR to exercise is another useful parameter to evaluate vascular resistance, endothelial dysfunction indicating sympathetic dysfunction[32]. It has been shown[39] that cardiovascular reactivity to isometric or dynamic exercise is one of the most important markers in predicting the risk of developing hyper-

tension in the future. Filipovský et al[40] reported that in addition to the risk of developing hypertension in the future, EBPR was an important predictor of cardiovascular mortality. In our study, we observed 10.8% EBPR in the study group and there was no patient with EBPR in the control group.

As metabolic parameters, high uric acid levels are closely associated with cardiovascular diseases (CVD) such as hypertension, metabolic syndrome, heart failure and stroke. According to a recent study[41], age of onset of hyperuricemia was a significant predictor of CVD and risk of all-cause death, and those with onset of hyperuricemia at a younger age had a higher predictive power of mortality. In another study, a significant association was found between autonomic dysfunction, uric acid overproduction, and hypertension[42].

Study Limitations

Our study has several limitations. First of all, only asymptomatics or mild to moderate symptomatic patients were included. We excluded severely ill patients from the study because we believed that factors such as medications, positive pressure ventilation, prolonged hospitalization, and related psychomorbidity may have a confusing effect, even in the chronic phase. In addition, the sample size of the study was relatively small to provide sufficient statistical power to our findings. However, we believe that this preliminary report can provide an incentive for future research in this direction.

Conclusions

Our study suggests that COVID-19 is closely associated with autonomous sequelae in the long term. Based on the evidence to date of the long-term predictive power of HRR, EBPR, and high uric acid levels, this pilot study presents data on COVID-19-related autonomic dysfunction and these parameters may be frequently used in clinical practice to highlight the risk of future cardiovascular events and all-cause mortality.

Ethics Approval

Approved by the local ethics committee of Kirikkale University (Date: 27.01.2022, Decision number: 2022.01.30).

Informed Consent

Informed written consent was obtained from all participants.

Availability of Data and Material

Available.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Authors' Contributions

Concept – İ.H.İ, C.Ş; Design – İ.H.İ, C.Ş; Supervision – İ.H.İ. Materials – İ.H.İ.; Data Collection and/or Processing – İ.H.İ, C.Ş; Analysis and/or Interpretation – İ.H.İ, C.Ş; Literature Review – İ.H.İ., C.Ş.; Writing – İ.H.İ; Critical Review – İ.H.İ, C.Ş.

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