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The impact of long COVID on heart rate variability: a cross-sectional study

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Abstract

Background Long-term COVID-19 (LC), which may affect the autonomic nervous system (ANS), is the term for the symptoms that some patients had for an additional month after contracting the virus. Therefore, during the LC phase, ANS status was evaluated in patients with mild-to-moderate COVID-19 using heart rate variability (HRV), a measurement of ANS function.

Methods A cross-sectional research with 173 participants - both positive and negative for COVID-19 – was conducted. Based on self-reports, patients with COVID-19 were classified as to whether they had LC or not. A 5-minute ECG recorder and data detection and response report were used to measure the ANS.

Results There were notable age differences across the groups ($p=0.034$). Patients with LC under 25 years of age had a lower HRV categorized as a very-low-frequency (VLF) domain ($p=0.012$). Compared to the group without LC, a higher number of people in the LC group had aberrant autonomic neuroactivity ($p=0.048$).

Conclusion Mild-to-moderate patients with COVID-19 in young to middle age may develop autonomic dysfunction one month after infection.

Keywords Autonomic nervous system, Vagal nervous system, Long COVID-19, Heart rate

Introduction

Severe-acute-respiratory-syndrome-related coronavirus 2 (SARS-CoV-2) affects the cardiorespiratory, immune, endocrine, gastrointestinal, and nervous systems [1–3]. The SARS-CoV-2 may directly invade the brain via the ethmoid bone or olfactory bulb and is dependent on angiotensin-converting enzyme 2 (ACE2) receptors for intracellular penetration during acute infection [4]. In addition, indirect mechanisms due to cytokine storms (e.g., vasculitis, thrombosis, endothelial damage, inflammation, and immune response reaction to the viral infection of the central nervous system) are involved in neurological lesions [5–8]. Many patients who had mild or moderate symptoms of SARS-CoV-2 infection may have recovered, while some have continued to developing symptoms after their initial sickness. We defined persistent symptoms occurring more than four weeks after coronavirus disease 2019 (COVID-19) infection as long-COVID (LC) [9]. Long-term issues may influence COVID-19 survivors of all ages [10] and sexes [11, 12]. LC symptoms occur after 4–6 weeks of recovery from the initial illness and include fatigue, dyspnea, chest pain, and orthostatic pain [13].

Patients with LC frequently exhibit abnormalities in their neurological function [14]. Dysautonomia as a part of the LC symptom complex [15], has been linked to cognitive impairment [16] and a higher chance of fatal disease consequences [17]. The parasympathetic nervous

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system (PNS) and sympathetic nervous system (SNS), which have opposing roles, control one another, and maintain the balance of the autonomic nerves, make up the autonomic nervous system (ANS). Decreased heart rate variability (HRV), diminished vagal activity and dysregulated sympathetic activity are signs of ANS dysfunction in patients with LC [18, 19]. The likelihood that heart rate variability (HRV), a measure of ANS action, predicts LC has been reported in recent years [20, 21]. Measurement of HRV is a valuable method for assessing neurocardiac physiological status [22] produced by heart-brain interaction in a dynamic nonlinear autonomic nervous system [23]. The electrical activity of the heart, i.e. changes in a single heartbeat over time, is typically evaluated through electrocardiogram (ECG) testing [24]. The level of HRV is influenced by factors such as physical activity, stressful conditions, temperature [25], and personal mood. HRV can be seen as the heart's adaptive response to various stimuli, reflecting integrated regulation of physiological, psychological, and cognitive states. According to the study of Acharya et al., HRV detects and reacts to physiological changes, acting as a reflection of the ANS state [26]. Thus, in our study, HRV was used as an indicator to assess potential cardiovascular system disorders.

The occurrence of different COVID-19 complications is associated with sex and the total duration of illness [27]. As reported, women are more prone to high symptom loads of chronic stress, depression, anxiety, etc [28, 29]. , with subjective chemosensory dysfunctions (including anosmia and ageusia) being less common [30]. It has been suggested that the development of LC symptoms could be linked to autonomic dysfunction resulting from cytokine storms or immune-mediated [15, 31] inflammatory cytokines and coagulation excessive activation [32].

We observed that more data should be collected for research on ANS function in patients with LC, specifically for studies conducted one to twelve months following infection. This cross-sectional study aims to contribute evidence in this regard and guide future preventive and clinical interventions.

Methods

Study design and setting

Dongguk University in South Korea conducted a cross-sectional study on patients with LC from May 2022 to December 2023. Individuals between the ages of 18 to 50 make up the target population since they are the main working population in this age range. Simple random sampling was used without conditional matching, which could limit the unequal gender distribution.

Data collection

A total of 239 adults were recruited. Of 173 participants under the age of 50 years and over the age of 18 years were included in the study. Participants who visited the school health center gave their consent for this study to be carried out before the commencement. The participants were introduced to undergo an HRV survey in the same room at room temperature ranging from 26–28℃. Quiet conditions were maintained during the test. The short-term HRV parameters were recorded for 5 min using an ECG device in the school nurse's office (SA-3000P, Medicore, South Korea). The participants were then invited to complete a pre-assessment questionnaire for LC, which is provided as the supplementary file. The questionnaire was specially developed for this study, drawing upon definitions, primary symptoms, and patient assessments and management for LC as outlined by the World Health Organization [33], American Centers for Disease Control and Prevention [34], British National Health Service [35] and Australian Health Care Centre [36]. The questionnaire was initially designed and completed in the participant's native language, and we translated the responses into English during the subsequent data processing stage. Results lacking HRV reports or questionnaires were deemed low-quality and excluded from the study. Additionally, participants on medication or repeated reports were also excluded as shown in Fig. 1.

This study's final results comprised 173 participants, including 116 individuals who have a COVID-19 history and 57 healthy individuals. Of the 116 patients with COVID-19, 32 presented LC symptoms, including fatigue, cough, dyspnea, and dermatological allergic reactions. The study included three groups: group 1 comprised healthy participants without confirmed SARS-CoV-2 infection; group 2 comprised individuals who had recovered from COVID-19; and group 3 comprised patients with LC. The included participants were aged 22.5±5.88 years and included 43 males and 130 females.

HRV measurement

Both the frequency domain and the temporal domain are included in the HRV parameters. The variability of the inter-beat interval was used to get time-domain measurements [23]. The relative or absolute power in four-band distributions is measured in the frequency domain. The study's temporal domain contained the psychological stress index (PSI), the standard deviation of normal-to-normal (SDNN), and the root mean square of the successive normal (RMSSD), which characterizes parasympathetic high-frequency region activity. Additionally, using Fourier transform analysis, we gathered three distinct band powers: very low frequency (VLF = 0.003–0.04 Hz), low frequency (LF = 0.04–0.15 Hz), and high frequency (HF = 0.15–0.4 Hz). HF is a stand-in for the

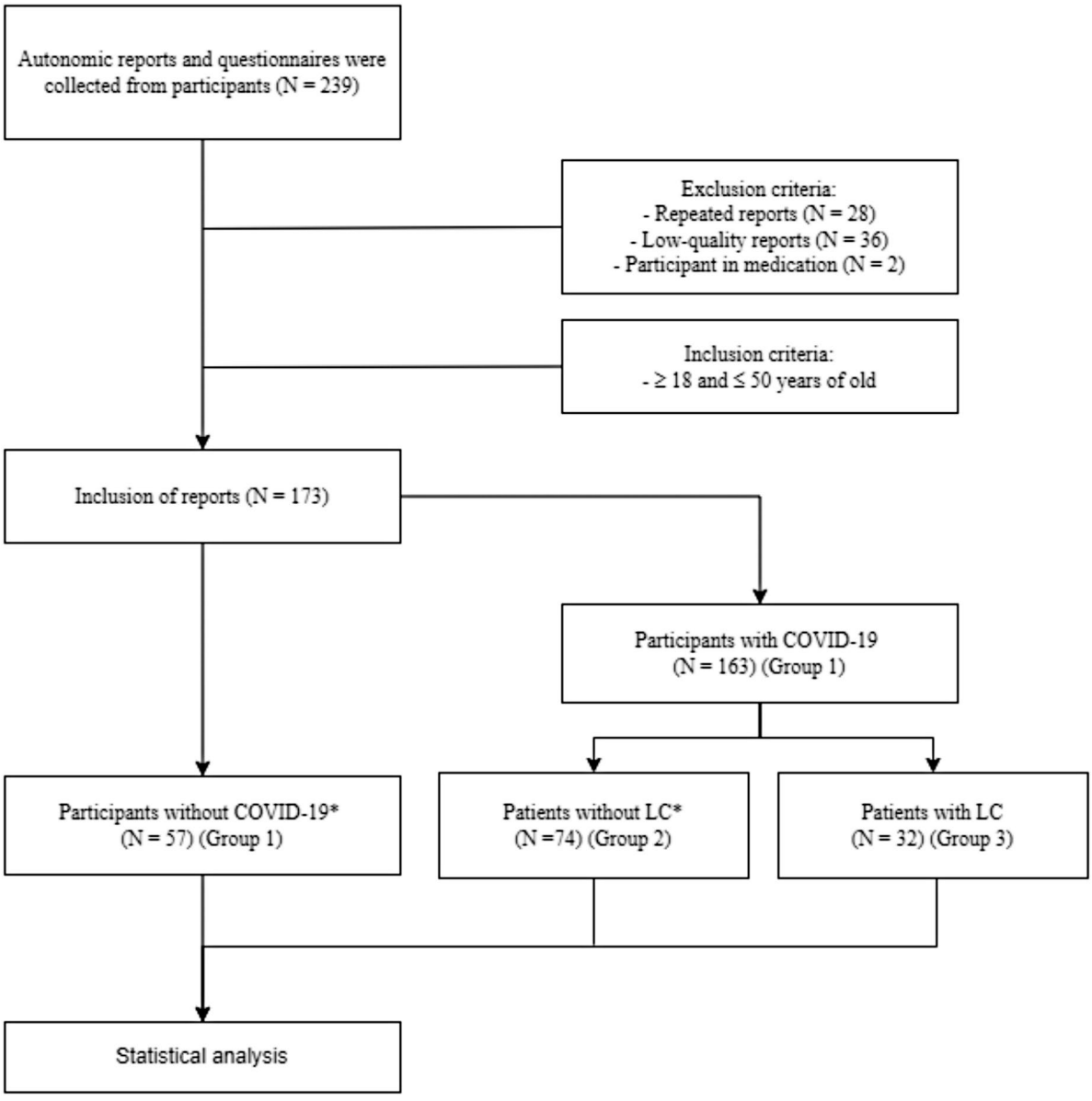

Fig. 1 Study selection. Cross-sectional Study, 2022–2023. A total of 239 reports were received. Of 66 reports were excluded as repeated reports from the same individual, reports missing heart rate variability survey section, or participants are on medication (Antihypertensive drugs and analgesics). Finally, 173 reports met the screening criteria which were categorized into three groups depending on the LC status. *COVID-19: coronavirus disease 2019; LC: long-term COVID-19

PNS in the frequency domain. A high LF denotes higher SNS activity, although the PNS or SNS might represent LF. An indicator of sympathetic/vagal balance is the LF/HF ratio [37]. Furthermore, there may be a correlation between VLF and SNS activity [38, 39]. Additionally, the HF frequency range can be used to measure vagal tone, which regulates HRV during the respiratory cycle [37].

The SA-3000P device performs an AI-driven three-minute HRV analysis and produces a data detection and response (DDR) report to evaluate the autonomic nervous system's balance. The DDR report covers various factors including autonomic activity, autonomic balance, autonomic stability, stress resistance, stress index, fatigue index, the mean heart rate, electrocardiac stability, and ectopia. Each factor is evaluated according to specific rating criteria (See Table S1).

Statistical analysis

Continuous data are represented as mean ± SDs and categorical data are expressed as percentages. The normality of continuous variables was first tested using the Shapiro-Wilk test. Student's t-test or ANOVA was used

for independent variables. The Mann-Whitney U test or Kruskal-Wallis rank-sum test was used for non-parametric variables. Categorical variables were tested via Pearson's chi-square test, the chi-squared test with Yates' continuity correction, Fisher's exact test, and the Kruskal-Wallis test. Statistical significance was set at a *P*-value of ≤0.05. Statistical analyses were performed via the R package (ver.4.3.2) and R-Studio software (5704.12.0.0).

Results

The research population consisted of 163 college students (94.22%), 1 postgraduate (0.58%), 1 teacher (0.58%), 3 assistants (1.73%), and 5 staff members (2.89%). Among the 173 participants, 116 had a COVID-19 history, with 84 recovering from the infection (72.41%) and 32 experiencing LC effects (27.59%). These participants were categorized into two groups: Group 2 included those with a history of COVID-19 but no LC symptoms, whereas Group 3 included those with LC symptoms. The remaining 57 healthy participants formed the control group (Group 1). Among the participants, three had been hospitalized (1.73%), and seven (4.05%) had underlying diseases, all of whom had a history of COVID-19. These conditions include hypertension, tuberculosis, pneumonia, migraine, and rhinitis. No underlying diseases were observed in the control group.

The participants' characteristics are presented in Table 1. There was an age difference among the study participants across the three groups ($p<0.05$), with observable distinction between participants with and without LC, particularly among 18–25 years of age ($p<0.001$). Additionally, the results revealed that patients with LC presented a greater likelihood of underlying disease ($p=0.044$) than participants without COVID-19.

Table 2 shows the HRV characteristics of each of the three groups, which suggested that individuals affected by LC had significantly different SDNN, VLF, and PSI ($p<0.05$) values than those in Group 2. Patients with LC exhibit a decreased SDNN and VLF, along with increased PSI, indicating dysregulated sympathetic activity and heightened autonomic stress. However, we did not observe differences in the DDR scale, possibly influenced by the confounding factor of age. Therefore, we conducted HRV analyses for various age groups, as presented in Tables 3 and 4.

All of the individuals' general characteristics were analyzed in Table 1, revealing significant differences in the age factor. No variations in ANS function were noted in general, nevertheless. To avoid age-related bias, we separately investigated HRV features in individuals aged < 25 years and ≥ 25 years. In line with the results from Tables 2 and 3 demonstrates a lower VLF among the patients with LC in Group 3 who were under 25 years of age ($p=0.012$), when compared to the patients without LC. The higher proportion of individuals with poor autonomic activity in this group may also explain the observed decrease in VLF. Conversely, Table 4 indicated no appreciable variations in HRV were observed among study participants aged ≥ 25 years old.

Table 1 General characteristics of study population ($n=173$)

Variable	Healthy controls (group1)	Patients without LC# (group2)	Patients with LC# (group3)	P1# (among group1-3)	P2#(between group1 and group3)	P3#(between group2 and group3)
	N = 57	*N* = 84	*N* = 32			
Age	22.2 ± 4.29	21.2 ± 2.52	26.8 ± 10.9	**0.034**[2)*]	**0.050**[6)]	**0.040**[6)*]
< 25	49(86.0)	80(95.2)	22(68.8)	**< 0.001**[3)**]	0.052[3)]	**< 0.001**[3)**]
≥25	8(14.0)	4(4.8)	10(31.2)			
Sex				0.676[3)]	0.420[3)]	0.403[3)]
Man	15(26.3))	22(26.2)	6(18.8)			
Woman	42(73.7)	62(73.8)	26(81.2)			
COVID-19 vaccine				0.846[4)]	0.630[4)]	0.530[4)]
Yes	53(93.0)	80(95.2)	30(93.8)			
No	4(7.0)	4(4.8)	2(6.2)			
Regular exercise				0.185[3)]	0.185[3)]	0.966[3)]
Yes	35(61.4)	39(46.4)	15(46.9)			
No	22(38.6)	45(53.6)	17(53.1)			
Underlying disease				0.051[4)]	**0.044**[4)*]	0.439[4)]
Yes	0(0.0)	4(4.8)	3(9.4)			
No	57(100.0)	80(95.2)	29(90.6)			
SBP#	120 ± 14.6	118 ± 12.6	116 ± 12.3	0.145[1)]	0.070[6)]	0.510[6)]
DBP#	71.6 ± 11.6	70.0 ± 11.6	73.0 ± 10.4	0.761[2)]	0.557[5)]	0.178[5)]

#: LC: long-term COVID-19; SBP: systolic blood pressure; DBP: diastolic blood pressure; P1: *p*-value of statistical analysis among group 1–3; P2: *p*-value of statistical analysis between group1 and group3; P3: *p*-value of statistical analysis between group2 and group3. *: $p<0.05$; **:$p<0.001$. Statistic methods: (1) ANOVA test; (2) Kruskal-Wallis H test; (3) PearsonPearsonVA test; 2) VA td group3. *:; P1: *p*-value of statistical analysisWhitny U test

Table 2 HRV assessment parameters of study population ($n = 173$)

Parameters	Healthy controls (group1)	Patient without LC[#] (group2)	Patients with LC[#] (group3)	P1[#](between group1-3)	P2[#](between group1 and group3)	P3[#](between group2 and group3)
	N = 57	*N* = 84	*N* = 32			
Time domain						
Mean HR[#]	83.4 ± 9.90	81.9 ± 14.0	81.2 ± 14.8	0.408[2)]	0.455[6)]	0.677[7)]
RMSSD[ms][#]	31.5 ± 16.5	35.2 ± 19.2	32.4 ± 19.9	0.517[1)]	0.847[7)]	0.442[7)]
SDNN[ms][#*]	40.0 ± 16.0	43.9 ± 16.4	37.7 ± 18.8	0.071[1)]	0.434[7)]	0.044[7)*]
Frequency domain						
PSI[#]	60.2 ± 57.6	61.6 ± 103	86.0 ± 98.8	0.071[2)]	0.502[7)]	**0.045[7)*]**
VLF[ms] [#*]	5.78 ± 1.06	6.00 ± 1.17	5.39 ± 1.19	0.021[2)*]	0.126[6)]	**0.015[6)*]**
LF[ms] [#]	5.72 ± 0.976	5.83 ± 1.09	5.45 ± 1.09	0.373[1)]	0.243[6)]	0.096[6)]
HF[ms] [#]	5.60 ± 1.15	5.66 ± 1.23	5.38 ± 1.35	0.503[1)]	0.429[7)]	0.306[6)]
LF Norm	52.9 ± 19.4	53.7 ± 21.5	52.0 ± 19.9	0.920[2)]	0.821[7)]	0.741[7)]
HF Norm	47.3 ± 19.2	46.0 ± 21.9	45.9 ± 22.6	0.732[1)]	0.847[7)]	0.991[6)]
LF/HF	1.69 ± 1.69	2.17 ± 2.85	1.48 ± 1.07	0.792[2)]	0.861[7)]	0.602[7)]
abnormal HR	0.544 ± 1.84	0.857 ± 2.73	0.438 ± 1.64	0.460[2)]	0.681[7)]	0.272[7)]
DDR scale[#]						
Autonomic neuroactivity	89.8 ± 15.1	92.4 ± 18.0	87.9 ± 17.9	0.080[2)]	0.626[7)]	0.096[6)]
Degree of Autonomic neuroactivity				0.063[3)]	0.851[3)]	0.111[3)]
Abnormal	35(61.4)	36(42.9)	19(59.4)			
Normal	22(38.6)	48(57.1)	13(40.6)			
Autonomic neural balance diagram	51.9 ± 33.8)	53.1 ± 41.8	53.1 ± 34.4	0.939[2)]	0.928[7)]	0.688[7)]
Degree of Autonomic neural balance diagram				0.866[3)]	0.630[5)]	0.626[3)]
Imbalance	31(54.4)	43(51.2)	18(56.2)			
Balance	26(45.6)	41(48.8)	14(43.8)			
Stress resistance	91.9 ± 13.4	94.6 ± 13.8	90.6 ± 17.4	0.167[2)]	0.765[7)]	0.133[7)]
Degree of Stress resistance				0.316[3)]	0.919[3)]	0.288[3)]
Abnormal	22(38.6)	23(27.4)	12(37.5)			
Normal	35(61.4)	61(72.6)	20(62.5)			
Stress index	104 ± 13.9	101 ± 16.9	106 ± 20.1	0.173[1)]	0.922[7)]	0.155[7)]
Degree of stress index				0.789[3)]	0.854[3)]	0.536[3)]
Abnormal	15(26.3)	19(22.6)	9(28.1)			
Normal	42(73.3)	65(77.4)	23(71.9)			
Fatigue	108 ± 20.2	105 ± 21.4	110 ± 19.1	0.280[2)]	0.768[7)]	0.179[7)]
Degree of fatigue				0.124[3)]	0.851[3)]	0.173[3)]
Abnormal	35(61.4)	38(45.2)	19(59.4)			
Normal	22(8.6)	46(54.8)	13(40.6)			
Average HR	83.3 ± 9.79	82.1 ± 14.1	81.7 ± 14.6	0.537[1)]	0.579[6)]	0.891[6)]
Degree of average HR				0.439[4)]	0.233[3)]	0.534[4)]
Abnormal	4(7.0)	12(14.3)	4(12.5)			

Table 2 (continued)

Parameters	Healthy controls (group1)	Patient without LC# (group2)	Patients with LC# (group3)	P1#(between group1-3)	P2#(between group1 and group3)	P3#(between group2 and group3)
	N = 57	*N* = 84	*N* = 32			
Normal	53(93.0)	72(85.7)	28(87.5)			
Cardiac stability	94.7 ± 18.4	97.4 ± 21.7	94.3 ± 22.4	0.816[2)]	0.936[6)]	0.563[7)]
Degree of Cardiac stability				0.893[3)]	0.635[3)]	0.749[3)]
Abnormal	22(38.6)	34(40.5)	14(43.8)			
Normal	35(61.4)	32(59.5)	14(66.3)			

LC: long-COVID; P1: *p*-value of statistical analysis among group 1–3; P2: *p*-value of statistical analysis between group1 and group3; P3: *p*-value of statistical analysis between group2 and group3; DDR scale: data detection and response; HR: mean heart rate; RMSSD: root mean square of the successive normal; SDNN: standard deviation of normal-to-normal; PSI: psychology stress index; TP: total power; VLF: very low frequency; LF: low frequency; HF: low frequency. *: $p < 0.05$. Statistical methods:1) ANOVA; 2) Kruskal-Wallis H test; 3) Pearson's chi-squared test; 4) Fisher's exact test; 5) Chi-squared test with Yates' continuity correction; 6) Student's t-test; and 7) Mann-Whitney U test

Discussion

This study examined HRV and autonomic homeostasis among students and staff at a South Korean university more than 4 weeks after contracting COVID-19. We defined this stage as LC from the National Institute for Health and Care Excellence. According to ANS evaluations, we identified patients with LC had a potential reduction in vagal activity and heightened stress levels. Notably, this tendency was observed only among participants under the age of 25, which could be related to the sample size, measurement difficulties, or the influence of underlying disease impact limits.

Previous studies have produced contradictory findings, with one study pointing to enhanced PNS activity as evidenced by higher HRV levels in patients with COVID-19 compared to healthy individuals following the acute infection phase [22], while other studies noticed decreased HRV levels in patients with a history of COVID-19 [20, 40–43]. The latter research predominantly evaluated patients 12 weeks after infection, whereas the former mostly focused on patients within 8 weeks of COVID-19 infection. This temporal mismatch may assist in explaining the gap in the results. Within 12 weeks of infection, there was an increase in SNS activity and the inhibition of PNS as a result of the mental stress and the virus's long-lasting consequences. Our study focuses on mild-to-moderate adults aged 18–50 years to evaluate their autonomic balance. The absence of severe COVID-19 patients is a fundamental feature of the study cohort. First, there was a notable age difference between the LC group under 25 years and the rehabilitation group, but no significant difference was observed compared with the healthy population. Apart from this distinction, no other significant differences were found in the general characteristics of the groups. Although young adults who presented with mild-to-moderate ANS disorders after post-COVID-19 had increased stress indices, lower HRVs, and global variability than healthy individuals did [44], we found no differences in HRV between the recovered group and the healthy group. This finding may be attributed to the predominant representation of young adults in our sample, which aligns with findings reported in the current literature [45–48].

The majority of participants in this study were women. While some studies have indicated that women may be at increased risk for LC [49–53], we observed no significant difference in the sex within the LC group in our present cohort. This difference appears to be due to the unequal gender distribution [54].

Building on the interpretation proposed by Freire et al. [47], the potential improvement in ANS abnormalities following mild-to-moderate SARS-CoV-2 infection in young adults potentially leads to recovery in HRV. Similar to our results, no differences were found in sex,

Table 3 HRV parameters of participants under 25 years old ($n=151$)

Parameters	Healthy controls (group1) $N=49$	Patient without LC[#] (group2) $N=80$	Patients with LC[#] (group3) $N=22$	P1[#] (between group1-3)	P2[#] (between group1 and group3)	P3[#] (between group2 and group3)
Time domain						
Mean HR[#]	83.7±9.95	81.5±13.9	82.0±14.9	0.552[1)]	0.716[6)]	0.838[6)]
RMSSD[ms] [#]	31.7±16.7	36.0±19.3	33.6±21.4	0.672[2)]	0.975[5)]	0.487[5)]
SDNN[ms] [#]	40.2±16.1	44.6±16.3	40.5±20.1	0.233[2)]	0.583[5)]	0.344[6)]
Frequency domain						
PSI[#]	60.5±58.5	58.0±99.0	78.7±92.9	0.159[2)]	0.462[5)]	0.091[5)]
VLF[ms] [#]	5.79±1.08	6.06±1.16	5.38±1.27	**0.031**[2)*]	0.060[6)]	**0.012**[5)*]
LF[ms] [#]	5.75±0.93	5.86±1.08	5.59±1.10	0.456[2)]	0.549[5)]	0.273[6)]
HF[ms] [#]	5.60±1.15	5.71±1.23	5.55±1.32	0.693[1)]	0.656[5)]	0.655[6)]
LF Norm	53.1±19.0	53.2±21.6	51.1±18.5	0.937[1)]	0.770[6)]	0.515[6)]
HF Norm	19.0±47.1	21.6±46.5	18.5±46.0	0.650[1)]	0.744[6)]	0.950[6)]
LF/HF	1.70±1.71	2.16±2.90	1.36±0.920	0.610[2)]	0.723[5)]	0.428[5)]
abnormal HR	0.564±1.87	0.888±2.80	0.565±1.93	0.496[2)]	0.997[5)]	0.452[5)]
DDR scale						
Autonomic neuroactivity	89.8±15.4	95.0(±17.8	88.0±19.2	0.072[2)]	0.415[5)]	0.127[6)]
Degree of Autonomic neuroactivity				0.056[3)]	0.607[3)]	**0.048**[3)*]
Abnormal	28(57.1)	32(40.0)	14(63.6)			
Normal	21(42.9)	48(60.0)	8(36.4)			
Autonomic neural balance diagram						
	51.3±33.4	54.7±42.0	34.2±34.2	0.982[1)]	0.823[5)]	0.896[5)]
Degree of Autonomic neural balance diagram				0.955[3)]	0.965[3)]	0.865[3)]
Imbalance	27(55.1)	42(52.5)	12(54.5)			
Balance	22(44.9)	38(47.5)	10(45.5)			
Stress resistance	91.8±13.7	95.2±13.6	91.9±18.4	0.930[1)]	0.737[6)]	0.450[6)]
Degree of Stress resistance				0.486[3)]	0.976[3)]	0.419[3)]
Abnormal	18(36.7)	22(27.5)	8(36.4)			
Normal	31(63.3)	58(72.5)	14(63.6)			
Stress index	104±14.1	100±16.4	106±20.5	0.201[2)]	0.580[5)]	0.126[5)]
Degree of stress index				0.886[3)]	0.660[3)]	0.640[3)]
Abnormal	11(22.4)	18(22.5)	6(27.3)			
Normal	38(77.6)	62(77.5)	16(72.7)			
Fatigue	108±20.4	105±21.6	111±19.1	0.280[2)]	0.538[5)]	0.146[5)]
Degree of fatigue				0.124[3)]	0.994[3)]	0.167[3)]
Abnormal	29(59.2)	34(42.5)	13(59.1)			
Normal	20(40.8)	46(57.5)	9(40.9)			
Average HR	83.6±9.84	81.7±14.0	82.5±15.0	0.680[1)]	0.836[6)]	0.791[6)]

Table 3 (continued)

Parameters	Healthy controls (group1)	Patient without LC[#] (group2)	Patients with LC[#] (group3)	P1[#] (between group 1-3)	P2[#] (between group1 and group3)	P3[#] (between group2 and group3)
	N = 49	*N* = 80	*N* = 22			
Degree of average HR				0.689[4)]	0.776[4)]	0.647[7)]
Abnormal	4(8.2)	11(13.8)	3(13.6)			
Normal	45(91.8)	69(86.3)	19(86.4)			
Cardiac stability	94.7±18.7	98.2±21.8	94.8±22.7	0.902[1)]	0.774[6)]	578[6)]
Degree of Cardiac stability				0.687[3)]	0.388[3)]	0.570[3)]
Abnormal	17(34.7)	31(38.8)	10(45.5)			
Normal	32(65.3)	49(61.2)	12(54.5)			

[#] LC: long-COVID; P1: *p*-value of statistical analysis among group 1–3; P2: *p*-value of statistical analysis between group1 and group3; P3:*p*-value of statistical analysis between group2 and group3; DDR scale: data detection and response; HR: mean heart rate; RMSSD: root mean square of the successive normal; SDNN: standard deviation of normal-to-normal; PSI: psychology stress index; TP: total power; VLF: very low frequency; LF: low frequency; HF: low frequency; *: $p < 0.05$. Statistical methods: (1) ANOVA test; (2) Kruskal-Wallis H Test; (3) Pearson's chi-squared test; (4) Chi-squared test with Yates' continuity correction; (5) Mann-Whitney U test; (6) Student's t-test; and (7) Fisher's exact test

RMSSD, LF, or HF between the study groups. Some studies have reported lower ventricular and arterial stiffness, better myocardial contractility, preserved organ innervation [55, 56], and increased sensitivity of vagal reflexes [57] in young adults. This evidence collectively suggests the potential for remedying autonomic system dysfunction in young adults.

Due to the measurement challenges and unclear change processes, the VLF band has not been included in or fully investigated in the most recent studies on LC-associated HRV. The VLF rhythms are thought to be generated through stimulating heart-afferent sensory neurons, with variations at rest potentially indicating changes in sympathetic activity [58]. Among the HRV metrics, VLF takes the longest to baseline [59], which could be one of the factors contributing to measurement challenges. Blood et al. discovered a favorable correlation between VLF and depression symptoms [60]. In our study, patients with LC have lower VLF levels than those without LC, suggesting a potential and ongoing enhanced risk of experiencing depressive symptoms four weeks after COVID-19 infection. According to earlier studies, the common HRV interpretations for short-term measures (5–10 min) are HF, LF, and its ratio [61]. These parameters are important, but we did not find any significant differences between the groups, suggesting that the analysis of VLF may be overestimated.

On the other hand, some studies reported that low VLF is related to chronic inflammation, and decreases in c-reactive protein (CPR) and Interleukin 6 (IL-6) levels were observed [62, 63]. Taylor et al. suggested that parasympathetic activity dominates very low-frequency RR-interval rhythms [64]. The frequency of efferent vagal nerve transmission to the heart fluctuates at very low respiratory rates. The adverse prognostic value of low VLF suggests reduced vagal-cardiac nerve trafficking. Our findings suggest that lower VLF and greater incidence of abnormal autonomic activity in long-COVID-19 patients under 25 years of age indicate a poorer ability to generate chronic inflammation in the body. Such long-term alterations in autonomic activity may be associated with persistent systemic inflammation, neurotropism, or procoagulation [65–67]. Interestingly, we didn't notice this difference in people who were older than 25. The limited sample size and the absence of a 24-hour measurement, which is necessary to accurately identify VLF [68], may have an impact on it. Additionally, the discrepancy in Table 1 shows that patients with LC who were older than 25 had more underlying disorders, which will have an effect on the HRV that led to this disparity between the two age groups. This data emphasizes how critical it is to focus on young people, especially those with LC, whose prognosis might be worse than previously thought. They might face academic stress on college, as

Table 4 HRV parameters of participants over 25 years old ($n = 22$)

Parameters	Healthy controls (group1)	Patient without LC[#] (group2)	Patients with LC[#] (group3)	P1[#](between group1-3)	P2[#](between group1 and group3)	P3[#] (between group2 and group3)
	N = 8	*N* = 10	*N* = 4			
Time domain						
Mean HR[#]	76.0±5.66	90.5±14.7	79.1±15.2	0.505[1)]	0.502[4)]	0.237[4)]
RMSSD[ms] [#]	25.4±6.08	19.5±7.08	29.3±15.9	0.147[1)]	0.157[4)]	0.133[4)]
SDNN[ms] [#]	35.6±15.2	29.4±11.4	30.4±13.4	0.908[2)]	0.628[4)]	0.690[5)]
Frequency domain						
PSI[#]	51.6±29.4	134.0±169	104±117	0.728[2)]	0.957[5)]	0.701[5)]
VLF[ms] [#]	5.57±0.003	4.97±1.03	5.42±1.01	0.228[1)]	0.231[4)]	0.377[4)]
LF[ms] [#]	4.95±2.30	5.28±1.18	5.10±1.04	0.936[2)]	0.957[4)]	0.912[5)]
HF[ms] [#]	5.70±1.38	4.63±0.72	4.94±1.39	0.910[1)]	0.932[4)]	0.556[4)]
LF Norm	46.5±37.6	64.5±16.0	54.3±24.3	0.622[1)]	0.656[4)]	0.464[4)]
HF Norm	53.5±37.7	16.0±35.5	24.3±45.7	0.621[1)]	0.655[4)]	0.464[4)]
LF/HF	1.48±1.74	2.34±1.66	1.80±1.41	0.870[2)]	0.550[5)]	0.650[4)]
abnormal HR[#]	0.0	0.25±0.5	0.11±0.33	0.608[2)]	0.228[5)]	0.607
DDR scale						
Autonomic neuroactivity	89.0±2.83	77.8±10.7	87.4±14.9	0.197[1)]	0.204[4)]	0.176[4)]
Degree of Autonomic neuroactivity				0.123[3)]	0.120[3)]	0.126[3)]
Abnormal	7(87.5)	4(100)	5(50.0)			
Normal	1(12.5)	0	5(50.0)			
Autonomic neural balance diagram	69.0±56.6	22.2±24.6	62.3±35.1	0.409[1)]	0.459[4)]	0.057[4)]
Degree of Autonomic neural balance diagram				0.650[3)]	0.520[3)]	0.280[3)]
Imbalance	4(50.0)	1(25.0)	6(60.0)			
Balance	4(50.0)	3(75.0)	4(40.0)			
Stress resistance	94.0±2.83	83.8±14.5	87.3±14.9	0.591[2)]	0.506[4)]	0.609[5)]
Degree of Stress resistance				0.858[3)]	0.520[3)]	0.545[3)]
Abnormal	4(50.0)	1(25.0)	4(40.0)			
Normal	4(50.0)	3(75.0)	6(60.0)			
Stress index	97.0±1.41	114.0±23.7	107.0±20.3	0.351[2)]	0.471[4)]	0.528[5)]
Degree of stress index				0.616[3)]	0.351[3)]	0.689[3)]
Abnormal	4(50.0)	1(25.0)	3(30.0)			
Normal	4(50.0)	3(75.0)	7(70.0)			
Fatigue	114.0±18.4	118.0±12.6	108.0±20.1	0.764[2)]	0.352[4)]	0.284[5)]
Degree of fatigue				0.403[3)]	0.437[3)]	0.210[3)]
Abnormal	1(50.0)	4(100.0)	6(66.7)			
Normal	1(50.0)	0(0.0)	3(33.3)			
Average HR	76.0±5.66	90.5±14.7	79.8±14.2	0.553[1)]	0.553[4)]	0.254[4)]
Degree of average HR				0.459[3)]	0.357[6)]	0.505[3)]

Table 4 (continued)

Parameters	Healthy controls (group1)	Patient without LC[#] (group2)	Patients with LC[#] (group3)	P1[#](between group1-3)	P2[#](between group1 and group3)	P3[#] (between group2 and group3)
	N = 8	*N* = 10	*N* = 4			
Abnormal	0(0)	1(25.0)	1(10.0)			
Normal	8(100)	3(75.0)	9(90.0)			
Cardiac stability	96.0±1.41	81.8±9.5	93.1±22.7	0.211[1)]	0.236[4)]	0.207[4)]
Degree of Cardiac stability				0.624[3)]	0.319[3)]	0.280[3)]
Abnormal	5(62.5)	3(75.0)	4(40.0)			
Normal	3(37.5)	1(25.0)	6(60.0)			

[#]LC: long-COVID; P2: *p*-value of statistical analysis between group1 and group3; P3:*p*-value of statistical analysis between group2 and group3; DDR scale: data detection and response; HR: mean heart rate; RMSSD: root mean square of the successive normal; SDNN: standard deviation of normal-to-normal; PSI: psychology stress index; TP: total power; VLF: very low frequency; LF: low frequency; HF: low frequency. Statistic methods:1) ANOVA test; 2) Kruskal-Wallis H test; 3) Fisher's exact test;4) Student t-test;5) Mann-Whitney U test; 6) Pearson's Chi-squared test

well as vagal-controlled cardiorespiratory and psychocognitive issues.

The study sample was selected from a homogeneous community and conducted the study in a school environment to guarantee credibility. However, a design like that would restrict its potential to be applied to a wide range of people. Additionally, although the findings regarding HRV with the SA-3000P device are debated, we rigorously controlled for variables leading up to testing. This machine utilizes AI technology to assess and diagnose autonomic balance, offering more precise and intuitive results on autonomic changes.

It is crucial to consider this study's several limitations. First, because the data were not gathered for the current investigation, the cross-sectional study design was impacted by recollection bias and hard-to-control confounding factors. Second, the time aspect of COVID-19 recovery makes it challenging to rule out bias because there is no reliable time record for disease infection and recovery. Third, it is difficult to extrapolate the results to a range of people, including individuals with varying educational backgrounds and vocations, due to the limited and homogeneous sample size. Lastly, we obtained the data from the participants without any means of assessing the information's dependability, which could cause the study's findings to be overinterpreted.

The health impacts of LC may be deeper for younger persons since they are less prone to have concomitant chronic conditions. Therefore, for attempts to improve the quality of life and reduce the burden through suitable therapies, a faster and more precise diagnosis of LC is required. Furthermore, this study recommends the application of non-invasive HRV testing instruments. To ensure the accuracy of the results studies could gather prospective cohort data and record, compile, and discuss HRV test results at various intervals (5–10 min or 24 h).

Conclusion

Young patients (ages 18–25) with LC show signs of autonomic nervous system dysfunction four weeks post-infection, suggesting that future research should concentrate on interventions and therapies to target autonomic dysfunction in young patients with LC. Non-invasive HRV measurement is helpful in assessing this dysfunction.

Abbreviations

SARS-CoV-2	Severe-acute-respiratory-syndrome-related coronavirus 2
COVID-19	Coronavirus disease 2019
LC	Long-term COVID-19
ACE2	Angiotensin-converting enzyme 2
HRV	Heart rate variability
ECG	Electrocardiogram
RT-PCR	Reverse transcription polymerase chain reaction
RMSSD	Root mean square of the successive normal
SDNN	Standard deviation of normal-to-normal
PSI	Psychological stress index

HF	High frequency
LF	Low frequency
VLF	Very low frequency
HR	Mean heart rate
DDR	Data detection and response
P	P-value
CPR	C-reactive protein
IL-6	Interleukin 6

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
All the authors were involved in the conceptualization and design of the study. S.Y., and K.L. were responsible for the preparation of data collection, and S.Y. and M.Q. contributed to subsequent analysis. M.Q. drafted the initial version of the manuscript, with all authors providing critical feedback and contributing to the subsequent revisions of the text.

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Data availability
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Informed consent was obtained from all the participants for their participation in this study. In accordance with the established procedures of the institutional IRB and with the 1964 Helsinki Declaration, prior explanation and consent were obtained from the subjects, and the study was conducted. All consent forms are received in writing and kept on file. The Institutional Review Board of DONGGUK UNIVERSITY approved the protocol (20220033).

Consent for publication
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Competing interests
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