Section: Physiology

Original Research Article

COMPARISON OF HEART RATE VARIABILITY BETWEEN POST COVID-19 AND CONTROLS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: COVID-19 affects multiple organ systems, including autonomic cardiovascular regulation. Heart rate variability (HRV) is a validated measure of autonomic function, yet few studies examine post-COVID patients with comorbidities. This study aimed to evaluate HRV parameters in post COVID-19 patients with and without comorbidities compared to healthy controls. **Materials and Methods:** Cross-sectional study of 150 participants (50 per group). HRV recorded using 5-minute lead II ECG. Time-domain (SDNN, RMSSD) and frequency-domain (LF, HF, LF/HF) indices were analyzed. Statistical significance was assessed with Student's unpaired t-test ($p<0.05$). **Results:** Both post COVID-19 groups had significantly reduced SDNN and HF vs controls ($p<0.05$). LF/HF ratio was elevated in patients with comorbidities ($p<0.05$). RMSSD and LF were not significantly different. **Conclusion:** Post COVID-19 patients exhibit autonomic dysfunction, especially sympathetic dominance in those with comorbidities. Long-term cardiovascular monitoring is recommended.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] The infection has been associated with multisystem involvement, particularly affecting the respiratory and cardiovascular systems. Emerging evidence suggests that COVID-19 may also affect the autonomic nervous system, potentially leading to alterations in cardiovascular regulation.

The virus enters the target cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is most abundant on the surface of type II alveolar cells of the lungs. COVID-19 is known for affecting the respiratory tract and cardiovascular system.[2] In COVID-19 patients, both sympathetic and parasympathetic nerve activities play a pivotal role in increasing the risk of life-threatening events.[3] It is also found that the reduction in parasympathetic activity reduces the neuro-vagal anti- inflammatory reflex to release the pro-inflammatory cytokines and contributing to cytokine storm.[3] COVID-19 Patients with comorbidities have deteriorating outcomes compared with patients without comorbidities.[4]

HRV is a simple and non-invasive, objective, and validated method for the assessment of autonomic nervous system. HRV analysis can be performed to detect alteration in autonomic function and prognosis of the diseases in COVID-19 patients.[5] Autonomic dysfunction may occur during the acute phase as well as recovered COVID-19 patients.[6] A study by Marques et al,[7] demonstrated that long COVID-19 patients showed reduced HRV compared with healthy controls and decreased sympathovagal balance in heart. These changes in long COVID-19 patients can be monitored to understand its involvement in cardiac autonomic modulation and detect possible cardiovascular changes for short- or long-term prevention. The long-term prognosis of the post COVID-19 patients in cardiovascular effects is still unknown.[7]

In addition, the presence of comorbidities conditions such as hypertension and diabetes mellitus has been associated with poorer outcomes in COVID-19 and may further influence autonomic function. However, studies evaluating cardiovascular autonomic function in individuals who have recovered from COVID-19, particularly in relation to comorbidities, remain limited.

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Therefore, the present study aimed to evaluate and compare heart rate variability as an indicator of cardiovascular autonomic function among post-COVID-19 individuals with comorbidities, post-COVID-19 individuals without comorbidities, and healthy controls.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Physiology in collaboration with the Departments of Endocrinology and Respiratory Medicine, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur, between August 2022 and July 2024. A total of 150 participants were recruited, comprising three groups: post-COVID-19 patients without comorbidities (n=50), post COVID-19 patients with comorbidities (n=50), and healthy controls (n=50).

Data collection: The data were collected from subjects attending the Outpatient Departments (OPDs) of Endocrinology and Respiratory Medicine, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, as well as from staff and students of JNIMS. Participants were recruited using a stratified random sampling method, wherein the study population was divided into three strata: post COVID-19 patients with comorbidities, post COVID-19 patients without comorbidities, and healthy controls. From each stratum, 50 participants were randomly selected, making a total of 150 subjects.

Sample size determination: The sample size was calculated using the formula n=Z2pq/e2, where Z=1.96 at 95% confidence interval, p=0.25 (prevalence of cardiovascular dysautonomia in post COVID-19 patients, according to a recently published study,[8] q=1−p=0.75, and allowable error e=0.07. The calculated sample size was 147, which was rounded to 150. Participants fulfilling the inclusion criteria were recruited consecutively from the Endocrinology and Respiratory medicine OPDs, JNIMS, Imphal, Manipur.

Inclusion criteria

Post-COVID-19 with comorbidities: Patients aged 20–65 years with confirmed COVID-19 (RT-PCR/TrueNat positive), at least 3 months post-negative RT-PCR, and with pre-existing diabetes mellitus and/or hypertension.

Post-COVID-19 without comorbidities: Patients aged 20–65 years, both sexes, with history of RT-PCR and/or TrueNat positivity, at least 3 months post-negative RT-PCR, and without diabetes mellitus or hypertension.

Controls: Age- and sex-matched individuals without history of COVID-19 infection (self-reported), without hypertension, diabetes, or other chronic/autoimmune diseases.

Exclusion criteria

In all groups we have excluded chronic lung disease, chronic heart disease, chronic kidney disease, autoimmune disorders, pregnancy, lactation, and use of medications affecting autonomic function.

HRV measurement: Short-term HRV was assessed according to Task Force guidelines using a 5-minute lead II ECG recorded with Lab Chart Pro v8.1.13 (AD Instruments, Australia) and Power Lab 26T system. ECG was acquired in a sitting posture under controlled ambient temperature (23–25°C) after 10 minutes of rest.[9]

Participants were instructed to remain awake, calm, and avoid movements during recording. Frequency-domain parameters [low-frequency (LF: 0.04–0.15 Hz), high-frequency (HF: 0.15–0.40 Hz), LF/HF ratio] and time-domain parameters [SDNN, RMSSD] were analyzed using Lomb–Scargle periodogram. ECG data were processed using Lab Chart HRV module.

Data analysis

Statistical analysis was performed in SPSS v23. Descriptive statistics (mean ± SD, percentage) were used for demographic profile, basal blood pressure and basal heart rate of all subjects. Student's unpaired t-test were applied for comparison between controls and COVID-19 without comorbidities, and controls and COVID-19 with comorbidities. A p-value <0.05 was considered statistically significant at 95% CI.

Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee, JNIMS. Written informed consent was obtained from all participants prior to study enrolment.

RESULTS

A total of 150 participants were included in the study between August 2022 and July 2024, comprising 50 healthy controls, 50 post-COVID-19 patients without comorbidities, and 50 post-COVID-19 patients with comorbidities.

Table 1: Demographic and Anthropometric Characteristics

Variables	Range	Mean ±SD
Age (years)	25-65	39.61±11.81
Weight(kg)	50-100	61.55±11.87
Height(cm)	138-180	158.97±14.56
BMI (kg/m^2)	19-40	28.53±5.97

The demographic and anthropometric characteristics of the study population are presented in Table 1. The overall mean age of the participants was 39.61 ± 11.81 years. The mean body weight, height, and body mass index were 61.55 ± 11.87 kg, 147.97 ± 14.56 cm, and 28.53 ± 5.97 kg/m², respectively.

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Table 2: Age Distribution

Age (Years)	Controls	Patients without comorbidities	Patients with comorbidities	Total
< 25	8 (16%)	3 (6%)	0 (0%)	11(7.33%)
25-65	42 (84%)	47 (94%)	50 (100%)	139 (92.67%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)
Mean	34.6± 9.86	34.7± 8.44	49.52± 10.27	39.61± 11.81

The age distribution of the study population is shown in [Table 2].

Most participants belonged to the 25–65 years age group, representing most subjects across all three groups. The mean age was comparable between the control group and patients without comorbidities, whereas participants with comorbidities were relatively older.

Table 3: Gender Distribution

Gender	Controls	Patients without comorbidities	Patients with comorbidities	Total
Male	26 (52%)	28 (56%)	25 (50%)	79 (52.7%)
Female	24 (48%)	22 (44%)	25 (50%)	71 (47.3%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

The gender distribution of the participants is presented in [Table 3].

The study population showed a nearly equal distribution between males and females, with a slightly higher proportion of males overall. The distribution of gender was comparable across the three study groups.

Table 4: Basal Cardiovascular Parameters

Variables	Range	Mean ±SD
Basal SBP (mmHg)	100-160	124±11.57
Basal DBP (mmHg)	60-96	81.67±6.539
Basal HR (bpm)	60-100	79.306±9.035

Note: SBP-systolic blood pressure, DBP- diastolic blood pressure and HR- heart rate

The basal cardiovascular parameters of the participants are summarized in [Table 4].

The mean basal systolic and diastolic blood pressure and heart rate were within normal physiological ranges for the study population.

Table 5: Comparison of HRV parameters

Variables	Controls	Without Comorbidity	p value
SDNN (ms)	48.15±17.25	44.62±20.89	0.011*
RMSSD (ms)	39.03±18.76	34±14.2	0.158
High Frequency (ms2)	462.86±291.67	450.77±321.67	0.033*
Low Frequency (ms2)	446.59±289.81	406.87±268.6	0.532
LF/HF ratio	1.13±0.79	1.06±0.79	0.627

The comparison of heart rate variability (HRV) parameters between healthy controls and post-COVID-19 patients without comorbidities is shown in [Table 5]. A significant reduction in SDNN and HF power was observed in post-COVID-19 patients without comorbidities compared with healthy controls, while other HRV parameters did not show significant differences.

Table 6: Comparison of HRV parameters

Variables	Controls	Comorbidities	p value
SDNN (ms)	48.15±17.25	38.55±19.59	0.036*
RMSSD (ms)	39.03±18.76	33.28±21.56	0.134
High Frequency (ms2)	462.86±291.67	335.8±316.33	0.013*
Low Frequency (ms2)	446.59±282.81	375±291.19	0.473
LF/HF ratio	1.13±0.79	2.08±1.99	0.016*

The comparison between healthy controls and post-COVID-19 patients with comorbidities is presented in [Table 6].

Patients with comorbidities demonstrated a significant reduction in SDNN and HF power, along with a significant increase in the LF/HF ratio, indicating greater autonomic imbalance. No statistically significant differences were observed for RMSSD and LF power.

DISCUSSION

IThe findings of the present study demonstrate that individuals who have recovered from COVID-19 exhibit alterations in heart rate variability parameters when compared with healthy controls. Reductions in SDNN and HF power observed in post-COVID-19 participants suggest a decrease in parasympathetic (vagal) modulation of cardiac autonomic function. These alterations were more pronounced among post-

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COVID-19 patients with comorbidities such as hypertension and diabetes mellitus, as reflected by the significant reduction in SDNN and HF power along with an increase in the LF/HF ratio. These findings are consistent with previous studies reporting autonomic imbalance and reduced vagal activity following SARS-CoV-2 infection. The results of the present study therefore support the hypothesis that COVID-19 may have a persistent impact on autonomic nervous system regulation, particularly in individuals with underlying comorbid conditions.

COVID-19 is increasingly recognized not only as a respiratory disease but also as a condition with widespread systemic effects involving the cardiovascular and autonomic nervous systems. Both sympathetic and parasympathetic pathways play a central role in maintaining cardiovascular homeostasis, and disturbances in this balance may predispose individuals to adverse cardiovascular outcomes. Heart rate variability (HRV) provides a non-invasive tool for assessing autonomic regulation of cardiac function. In the present study, HRV parameters were compared among post-COVID-19 patients with comorbidities, post-COVID-19 patients without comorbidities, and healthy controls.

The findings of the present study demonstrated alterations in HRV parameters among individuals who had recovered from COVID-19 compared with healthy controls. SDNN was significantly reduced in both post-COVID-19 groups, suggesting a reduction in overall autonomic modulation. In addition, the reduction in high-frequency (HF) power observed among post-COVID-19 participants indicates decreased parasympathetic (vagal) activity. Furthermore, patients with comorbidities exhibited a higher LF/HF ratio, suggesting a relative predominance of sympathetic activity and disturbed sympathovagal balance. These alterations were more pronounced among individuals with comorbid conditions such as hypertension and diabetes mellitus.

These observations are consistent with previous studies that reported reduced SDNN and HF components in individuals recovering from COVID-19, suggesting impaired autonomic regulation.[10,11] Similarly, other investigations have demonstrated reduced parasympathetic modulation in recovered COVID-19 patients, even several months following infection.[12,13] However, some studies have reported divergent findings, including increases in certain HRV indices or varying patterns of sympathovagal imbalance.[6,14,15] Such differences may be attributed to heterogeneity in study populations, variations in comorbidity profiles, differences in the timing of post-COVID-19 assessment, and methodological differences in HRV measurement protocols.

Several mechanisms have been proposed to explain autonomic involvement in COVID-19. SARS-CoV-2 may affect neural tissues through receptors such as angiotensin-converting enzyme-2 (ACE2), neuropilin-1, and transmembrane serine proteases.[3] It has been hypothesized that the virus may access central autonomic structures through vagal pathways and potentially influence brainstem autonomic regulation.[16] These mechanisms may contribute to the alterations in autonomic balance observed following infection.

However, several factors should be considered when interpreting the findings of the present study. Differences in age between groups, levels of habitual physical activity, the use of antihypertensive or antidiabetic medications, and variability in the severity of previous COVID-19 infection may influence HRV measurements and could have acted as potential confounders.

Furthermore, the cross-sectional design of the present study and the absence of pre-infection baseline HRV measurements limit the ability to determine causal relationships or the temporal persistence of autonomic alterations. Therefore, the present findings should be interpreted as demonstrating an association between previous COVID-19 infection and HRV changes rather than establishing causality. Longitudinal studies are needed to further clarify the long-term impact of COVID-19 on autonomic regulation.

CONCLUSION

The present study suggests that individuals recovering from COVID-19 may exhibit alterations in heart rate variability parameters compared with healthy controls, indicating possible changes in autonomic regulation. Reduced parasympathetic activity and altered sympathovagal balance were more pronounced among participants with comorbidities such as hypertension and diabetes mellitus. These findings indicate a potential association between previous COVID-19 infection and altered cardiac autonomic function. However, due to the cross-sectional design of the study, causal relationships cannot be established. Further large-scale longitudinal studies are needed to better understand the long-term effects of COVID-19 on autonomic nervous system function.

Limitations and confounding factors

This study has several limitations that should be considered when interpreting the findings. First, the cross-sectional design limits the ability to establish causal relationships between previous COVID-19 infection and alterations in HRV. Second, although efforts were made to match participants by age and sex, minor differences in mean age remained between groups. Third, information on physical activity levels and lifestyle factors was not fully controlled, which may influence autonomic function. Finally, the severity of previous COVID-19 infection was not stratified, which could potentially affect HRV outcomes.

Several potential confounding factors may have influenced the results of the present study. Age differences between groups, levels of physical

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activity, and the use of medications such as antihypertensive or antidiabetic drugs may affect autonomic regulation and HRV. Additionally, variations in the severity of previous COVID-19 infection could contribute to differences in autonomic function. These factors represent potential confounders and should be taken into account when interpreting the findings of the present study.

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Ethics Approval and Informed Consent

This study was conducted according to the ethical standards of the institution and/or national research committee and in compliance with the Declaration of Helsinki (2013 revision). The study protocol was reviewed and approved by Institutional Ethics Committee, JNIMS and written informed consent was obtained from all participants prior to inclusion in the study.

Patient Consent for Publication

Not applicable. The study did not involve individual patient data/images identifiable in the manuscript. All participants provided informed consent for participation.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. No publicly archived datasets were used.

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