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Original Article

The Long-Term Impact of Covid -19 on Cardiac Autonomic Function in Young Adults Assessed by Heart Rate Variability

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ABSTRACT

INTRODUCTION: COVID - 19 had created long term impact on recovered patients in various systems of the body and it is termed as Long Covid. Involvement of autonomic nervous system in long covid patients can lead to dysfunction of vital organs including the cardio vascular system. Heart Rate Variability (HRV) is a non invasive measure of autonomic function that facilitates identification of Long covid patients at risk of developing cardiovascular complications.

AIM: To assess the long term impact of COVID -19 on cardiac autonomic function in young adults using Heart Rate Variability.

Methods: It is an observational and comparative study comprising of two groups. Group 1 (unaffected by COVID -19) and Group 2 (recovered from COVID -19, minimum of three months gap after infection at the time of recruitment and Real time Polymerase Chain Reaction (RT - PCR) for Covid -19 tested positive). Age and Gender matched for both the groups. Anthropological measurements were taken. The short term HRV was recorded in Research lab, Department of Physiology, DSMCH. Cardio vascular parameters like Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) were measured and compared between two groups.

HRV parameters:1. Time Domain Parameters like Mean Heart Rate (Mean HR), (SDNN), (RMSSD) and (PNN50) were measured and compared between two groups.

2. Frequency Domain Parameters like Low Frequency (LF nu), High Frequency (HF nu) and LF/ HF ratio were measured and compared between two groups.

Data was analyzed using JASP Software version: 0.19.3. Statistical analysis tests used were Mann Whitney U test and Odds ratio analysis.

Results: HRV showing statistically significant lower Time domain parameters like SDNN (P value : < 0.018) and RMSSD (P value : < 0.046) in the Group - 2 individuals which indicates that the parasympathetic activities were decreased in them.

Conclusion: Our study results showed decreased parasympathetic activity in Group - 2 than Group -1 individuals. There is a long term impact of Covid - 19 on cardiac autonomic function causing cardiac dysautonomia. Early diagnosis of cardiac dysautonomia due to COVID -19 in young adults can prevent incidence of cardiac morbidities and mortalities in future.

Keywords*: COVID 19, cardiac autonomic function, Heart rate, Heart rate variability.*

INTRODUCTION

It has been observed that many people diagnosed with Long covid syndrome had autonomic dysfunction 1. The regulation and integration of internal organs is done by the autonomic nervous system. It helps in the adaptation of internal

environment to changes in the external environment2 . The relationship between COVID 19 and autonomic nervous system is due to cytokine storm response. The cytokine storm during COVID 19 infection leads to activation of sympathetic system inducing release of proinflammatory cytokines, conversely the stimulation of vagus nerve results in anti-inflammatory response 3. The over activation of the sympathetic or parasympathetic components of the autonomic nervous system is referred as"Dysautonomia". The patho-physiology of autonomic dysfunction in Long covid syndrome is due to the SARS - COV-2 virus having a high affinity for medulla oblongata, involving Nucleus Tractus Solitarius and ventrolateral medulla. Since these areas have high ACE -2 receptors. Though respiratory tract is the major target for SARS - COV -2 Virus. Cardiovascular involvement has also been reported in post covid patients. It is very important to diagnose cardiac dysautonomia in general population, because in cardiac dyasautonomia / cardiac autonomic neuropathy, there is a defect in the sympathetic and parasympathetic supply of the heart which leads to arrhythmias, coronary vessel ischemia and sudden death syndrome. Mostly, Cardiac dysautonomia remains subclinical and present as altered Heart Rate Variability. In early phase, it may present as resting tachycardia and in advanced stage, it may cause exercise intolerance, cardiomyopathy with left ventricular dystrophy, orthostatic

NEED FOR MEASURING CARDIAC AUTONOMIC FUNCTION USING HEART RATE VARIABILITY IN POST COVID YOUNG ADULTS:

Several clinical manifestations have been documented in Long covid syndrome patients. But their impact on cardiovascular and autonomic nervous system in a younger population remain unclear. Thus, this study was conducted to examine whether there is any alterations in cardiac autonomic function in young individuals who were affected with Covid -19 in the past 4. Appropriate clinical checkup could be needed in future for Long covid cases who had cardiac dysautonomia which in turn helps us to prevent the incidence of myocardial infarction, coronary artery disease, sudden death and also aids in early diagnosis and
treatment 5.

MATERIALS AND METHODS

STUDY DESIGN: It is an observational & cross sectional study. The study was conducted in the Research laboratory of Department of Physiology, Dhanalakshmi Srinivasan Medical college and Hospital, Siruvachur, Perambalur.. This study was conducted from August 2023 to July 2024.

The sample size calculation led to the formation of two groups Group I cases without COVID 19 (50 cases
Group II cases with COVID 19 (50 cases)

METHODOLOGY:

Total of 100 young adults of both male and female aged between 18 and 30 years were selected . Out of 100 subjects , 50 were categorized as Group 1(Never been diagnosed covid with RT - PCR) and other 50 were Categorized as Group 2 (RT PCR Positive for Covid -19). Gender was matched between two groups . In Group 1 , 25 males and 25 females were recruited and in Group 2 also, 25 males and 25 females were recruited. Both the groups were clearly explained about the study procedure, a written informed consent was obtained from study subjects. They were asked to fill the data proforma consisting of demographic details and clinical history. After clinically examining the participants, height was measured in (cm) ,weight in (kg) and BMI was measured using quetelets index (BMI = weight (Kg) / height (m2)) . Waist circumference was measured as (cm) at the level of umblicus.

Cardiovascular parameters like Blood pressure and Pulse rate was measured and noted. HRV recording was done in a calm room at an optimum temperature(23 - 28 degree) without any bright light and noise .Subjects were asked to sit and relax for 5 minutes . ECG limb leads were placed and connected to the HRV recorder. Audacity software was opened , recording was done for continous duration of 2 minutes. Checked for any artifacts in the RR Tachogram. Then the RR Tachogram is transmitted to the Kubios software which analyses the beat to beat variability of the participants. Finally, Time domain and Frequency domain parameters of HRV were estimated. In Time domain analysis, rMSSD, pNN50, sDNN and Mean HR were measured. In Frequency domain analysis, LF, HF, LF/HF ratio were measured.

STATISTICAL ANALYSIS

Non Parametric test Mann Whitney U Test was used to compare the difference between two independent variable. Here, P- Value < 0.05 taken as significant * and P- Value <0.01taken as highly significant .Study parameters for both the groups were represented using Box and whisker plot. Risk ratio and Odds ratio for low SDNN and low RMSSD were estimated.

In the present study, based on selection criteria, (mentioned in the materials and methods) , the subjects were recruited and their history was recorded in the data proforma. A total of 100 Participants were recruited in the study. Out of 100 subjects, 50 subjects had no history of RT PCR Positive Covid -19 infection in the past and named as GROUP 1. Another 50 subjects had history of Covid -19 infection in the past and they were tested RT PCR positive for Covid -19 infection and named as GROUP 2 .

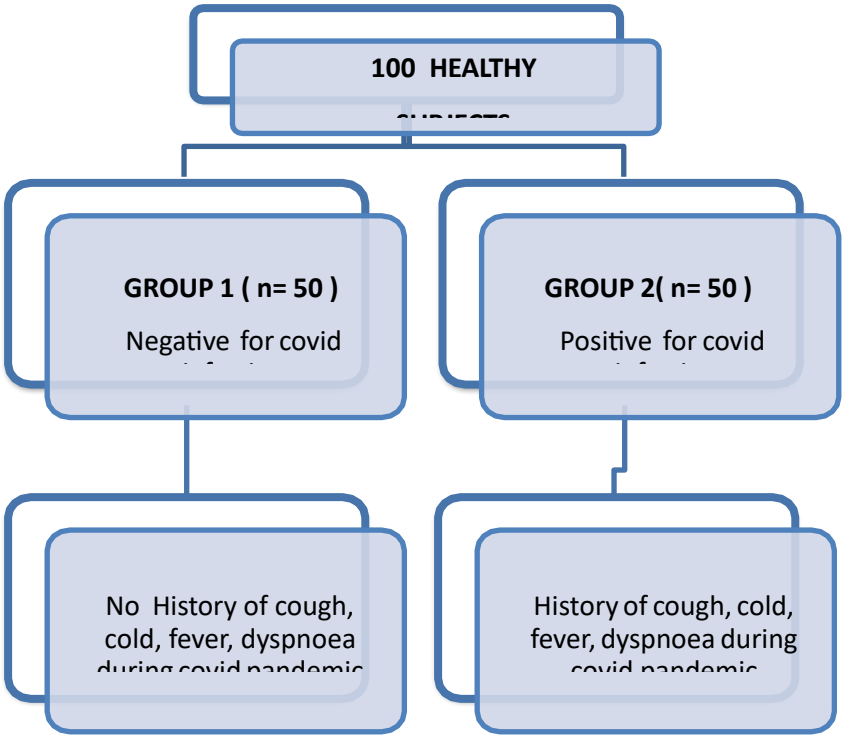


Figure 1 showing recruitment process of participants in the study .

The age group of the participants (n= 100) was from 18 to 30 years. Out of 100 participants, 50 were males and 50 were females. In group 1, there were 25 Covid negative males and 25 covid negative females .As seen in Figure no.6 and 7, In group 2 , there were 25 Covid Positive males and 25 covid positive females.

A detailed history regarding their year of covid infection was noted (2020,2021 ,2022) Among group -2 participants , 28 % got diagnosed with COVID - 19 in the year of
2020, 56 % got diagnosed in the year of 2021 and 26 % got diagnosed in the year of 2022 (Figure no .9). For both the groups , their vaccination history for Covid -19 vaccine was noted . In Group 1, 94 % of participants had vaccination against Covid -19 and In Group 2 , 96 % of Participants had vaccination against Covid – 19. .No subjects had been taking any drugs like Beta blockers , Theophylline and Sedatives during the study period. No Participants reported any history of sudden cardiac death in their family .

FIGURE NO. 2: showing gender distribution in group 1 individuals.

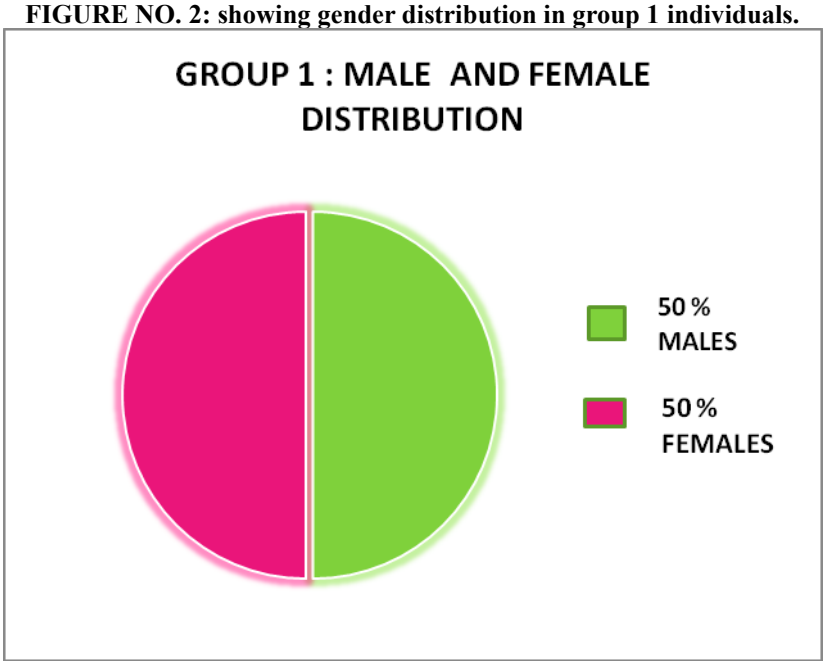


FIGURE NO . 3: showing gender distribution in group 2 individuals.

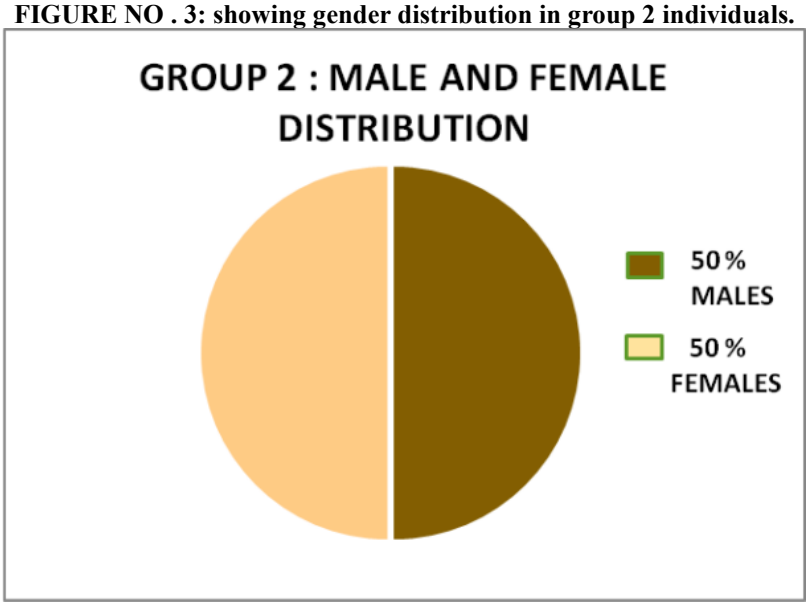


FIGURE NO.4: showing year of Covid infection in group -2 individuals.

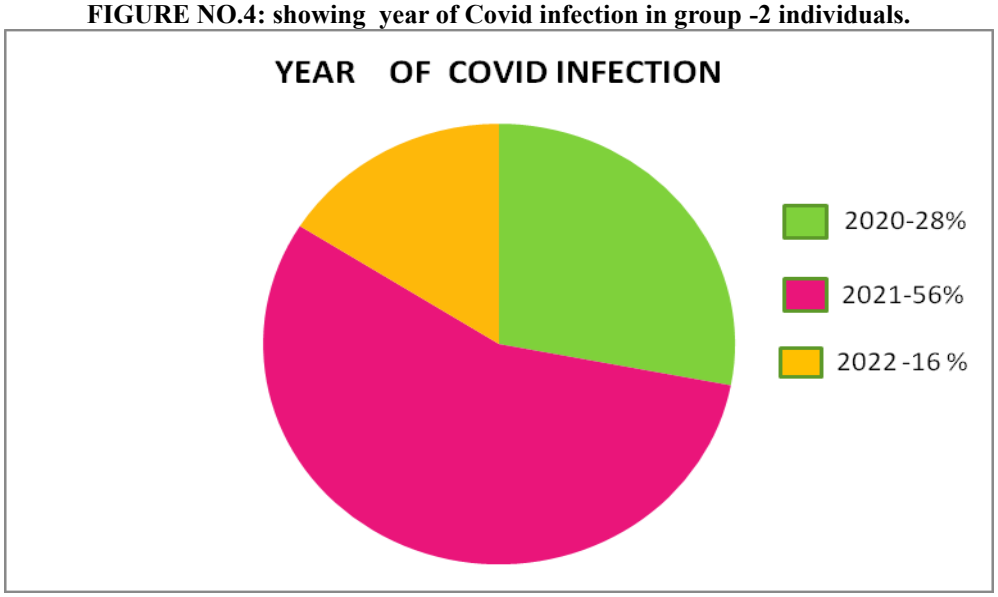


FIGURE NO. 5: showing percentage of vaccination against Covid - 19 in group - 1 individuals.

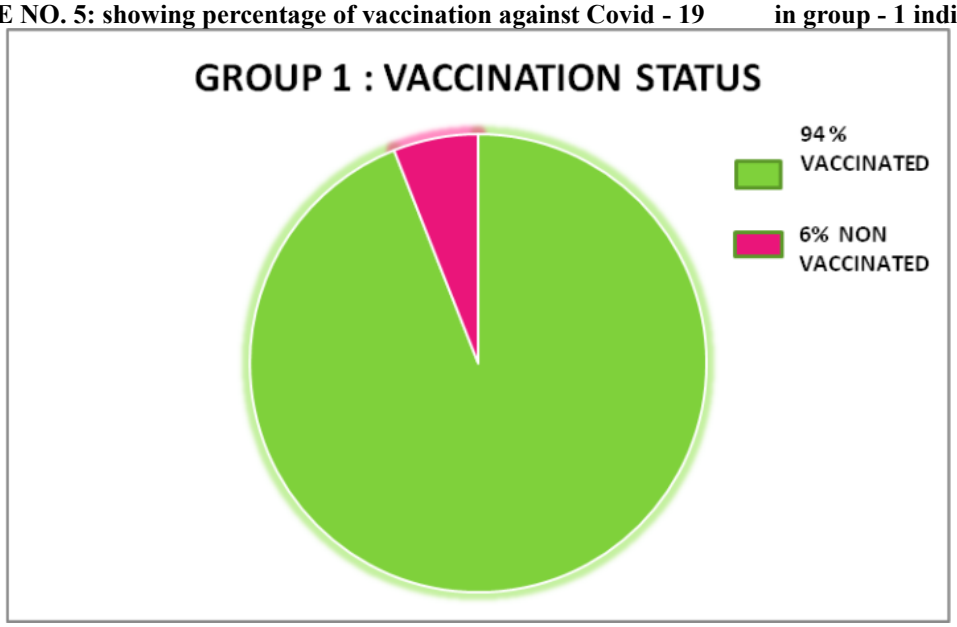


FIGURE NO.6: showing percentage of vaccination against Covid - 19 in group - 2 individuals .

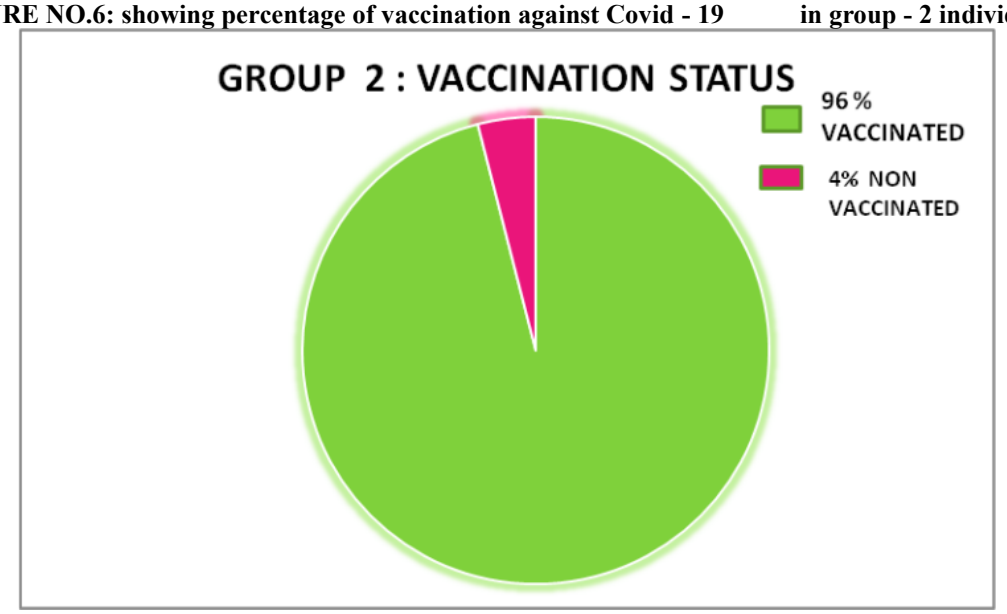


TABLE NO .1: Analysis of various anthropometric measurements in the study population (n = 100)

	AGE (years)	HEIGHT (cms)	WEIGHT (kgs)	BMI (kg /m^2)
MEAN	19	163.3	58.335	21.8
MEDIAN	19	164	57	21.24
IQR (75 th - 25 th percentile)	1(19 -18)	13 (168– 155)	18.25(67 - 48 .75)	5.75 (24.82 -19.06)
STANDARD DEVIATION	1.93	9.36	12.48	4.01
MINIMUM	18	141	30	15.09
MAXIMUM	30	188	95	32.44

OBSERVATION: Mean age of all participants was 19. Mean height was 163 .3 cm and mean weight was 58.335 kg . Mean BMI recorded was 21.8 kg /m2 .

TABLE NO . 52 : Comparisonof cardiovascular parameters (SBP, DBP, MAP & HR) among group - 1 and group - 2.

	GROUP	N	MEDIAN	IQR (75 th – 25 th percentile)	STD	P- VALUE
HR (Bpm)	GROUP 1 GROUP 2	50 50	76 78.5	9.5 (81.75-72.25) 11.75(82–70.25)	7.437 7.951	0.689
SBP (mmHg)	GROUP 1 GROUP 2	50 50	110 100	20 (120– 100) 20(110–90)	10.498 13.702	0.003 **
DBP (mmHg)	GROUP 1 GROUP 2	50 50	70 70	10 (80 – 70) 10 (70 – 60)	8.819 7.475	0.010 *
MAP (mmHg)	GROUP 1 GROUP 2	50 50	86.667 80	13.33 (93.33– 80) 10(83.33-73.33)	8.841 8.583	0.002**

(** highly significant)

OBSERVATION : Systolic blood pressure , Diastolic blood pressure and Mean arterial pressure was significantly higher in Group 1 subjects compared to Group 2 subjects .

FIGURE NO . 7: Box and whisker plot showing comparison of HR between group 1 and group 2 individuals.

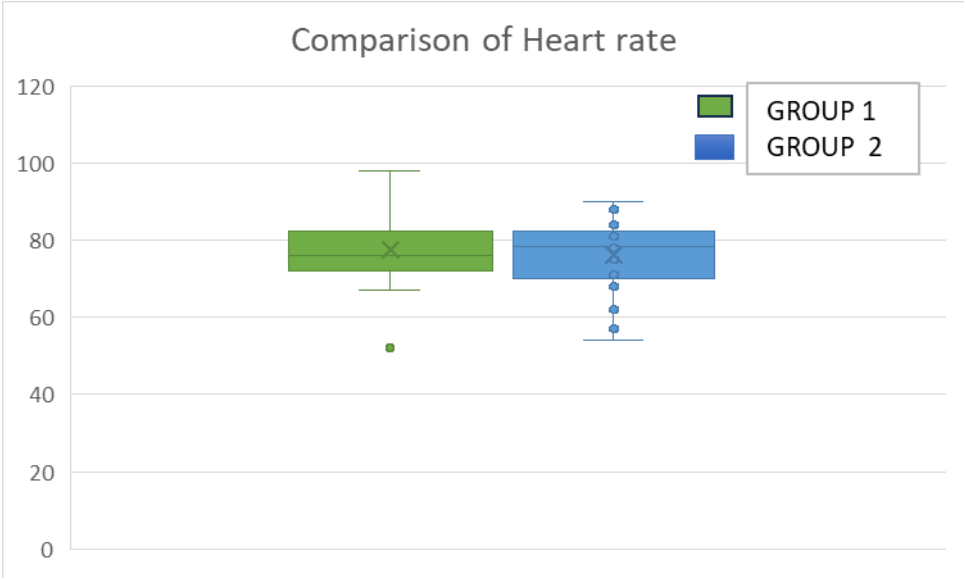


FIGURE NO . 8 : Box and whisker plot showing comparison of SBP between group -1 and group -2 individuals .

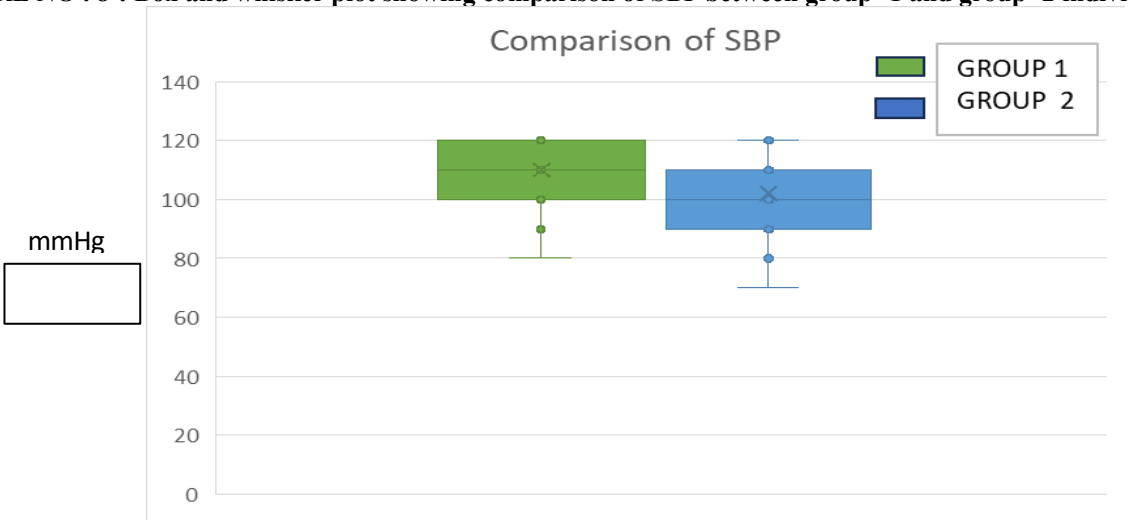


FIGURE NO . 9 : Box and whisker plot showing comparison of DBP between group 1 and group 2 individuals.

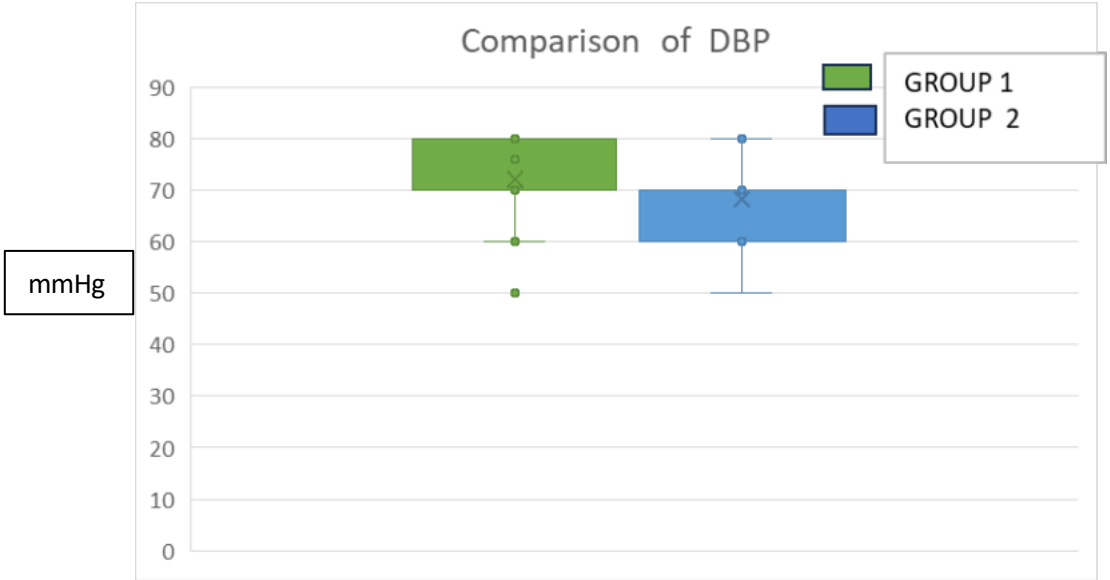
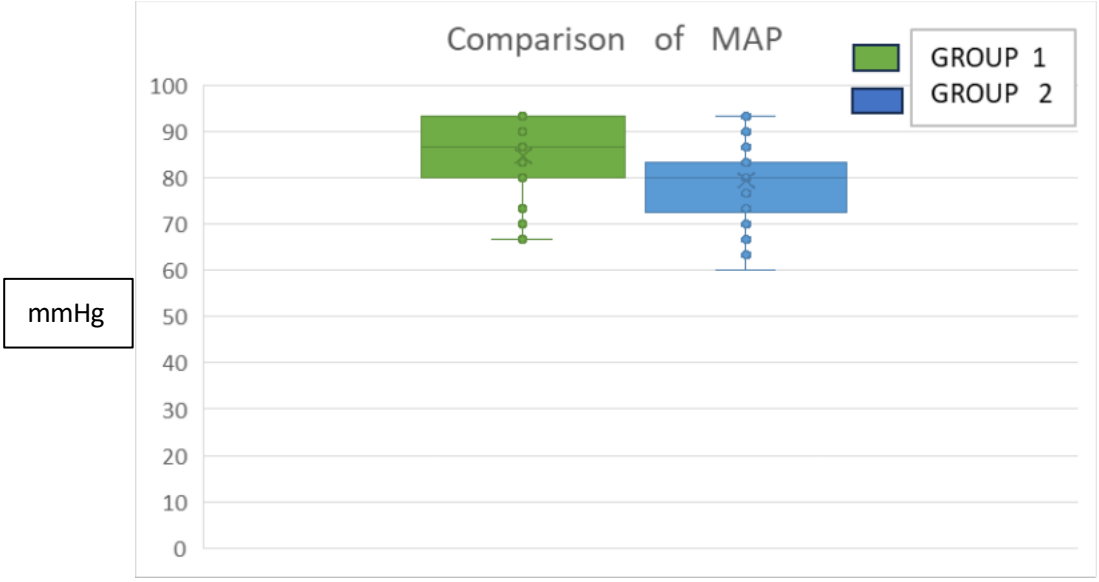


FIGURE NO .10 : Box and whisker plot showing comparison of MAP between group 1 and group 2 individuals.



OBSERVATION : There is significant difference of cardio vascular parameters among group 1 and group 2. Box and whisker plot showing significantly higher SBP, DBP
and MAP in group 1 individuals .

TABLE NO . 6 : Comparison of time domain parameters between group 1 and group 2.

PARA-METER	GROUP - 1		GROUP - 2		
	MEDIAN	**IQR (75 – 25 th Percentile)**	**MEDIAN**	**IQR (75 – 25 th Percentile)**	**P - VALUE**
MEAN HR (Bpm)	80.5	12 (86 -74)	83.5	13.5 (88 -74.5)	0.1
SDNN (ms)	49.85	22.6 (59.725 - 37.125)	42.2	12.85 (48.8 - 35.97)	0.018 *
RMSSD (ms)	51.7	29.825 (65.475 - 35.65)	41.8	15.35 (51.87-36.55)	0.046 *
PNN50 (%)	19.91	33.585(42.512-8.927)	18.78	18.95 (27.96-8.785)	0.156

(* significant)

OBSERVATION : Time domain parameters like SDNN , RMSSD were significantly lower in Group 2 subjects .
42

FIGURE NO . 11 : Box and whisker plot showing comparison of Mean HR between group 1 and group 2 individuals.

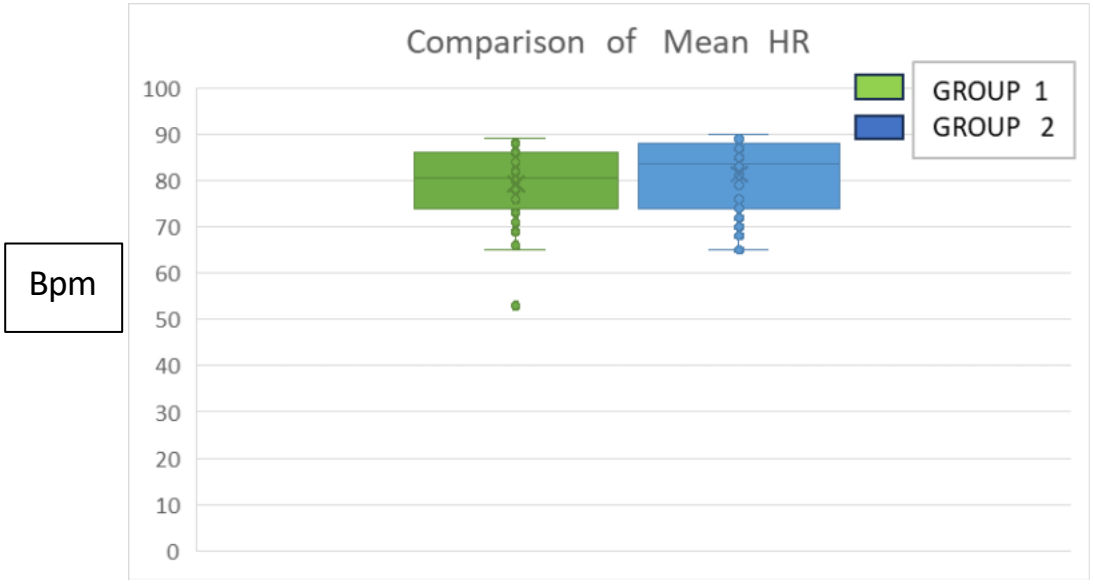


FIGURE NO . 12 : Box and whisker plot showing comparison of SDNN between group 1 and group 2 individuals .

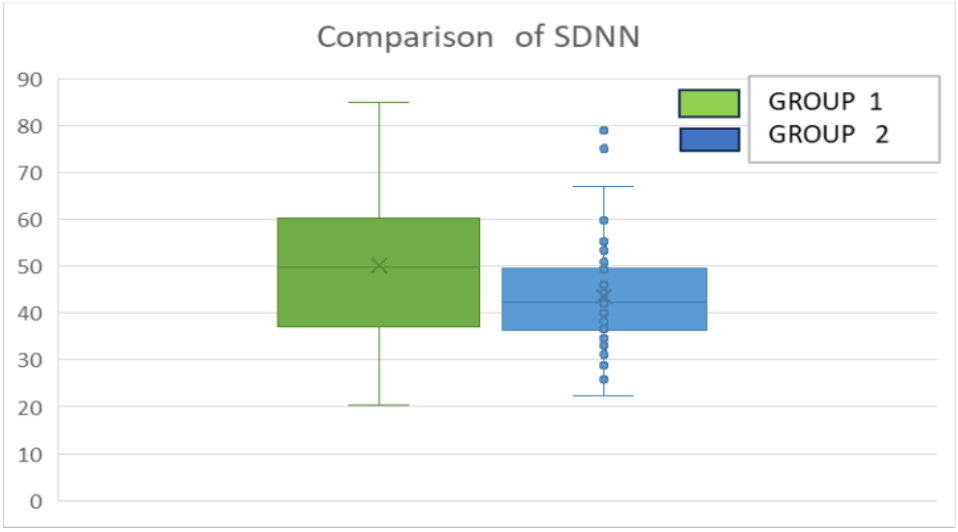


FIGURE NO .13: Box and whisker plotshowing comparison of RMSSD between group 1 and group 2 individuals .

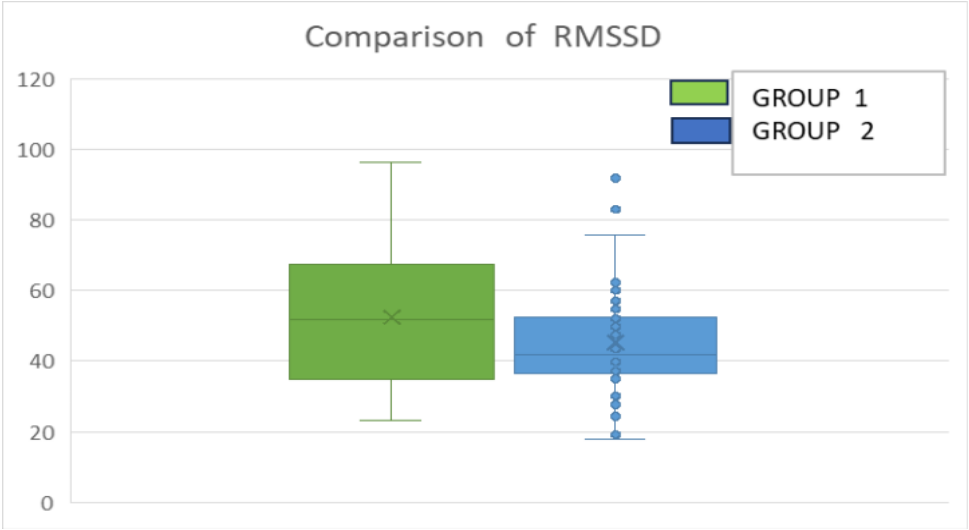
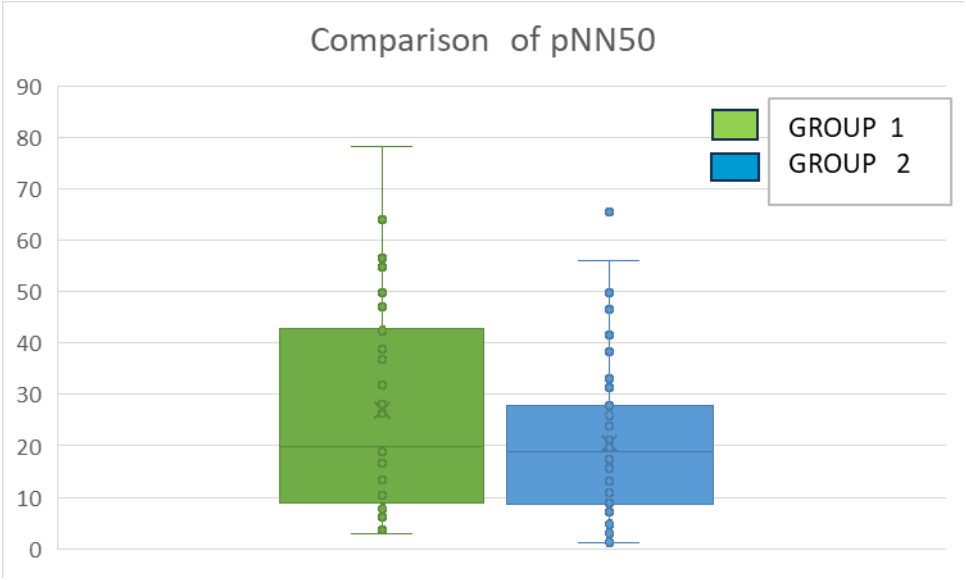


FIGURE NO . 14 : Box and whisker plot showing comparison of PNN50 between group 1 and group 2 individuals.



OBSERVATION : There is significant difference of Time Domain Paramerters between group 1 and group 2. Box and whisker plot showing significantly lower SDNN and RMSSD in group 2 individuals.

TABLE NO . 7 : Comparison of Frequency Domain Parameters between group 1 and group 2 .

Parameter	GROUP - 1		GROUP - 2		
	MEDIAN	**IQR (75 – 25 th Percentile)**	**MEDIAN**	**IQR (75 – 25 th Percentile)**	**P-VALUE**
LF nu	45.74	21.61 (57.26 - 35.65)	47.215	22.035(61.67 -39.63)	0.269
HF nu	54.2	22.063(64.76 - 42.70)	51.61	23.665 (60.24 – 36.58)	0.143
LF / HF ratio	0.85	0.751(1.337 - 0.586)	0.937	1.047 (1.705– 0.658)	0.29

OBSERVATION : Frequency domain parameters like LF nu, HF nu , LF / HF ratio were not showing significant differences .

FIGURE NO . 15: Box and whisker plot showing comparison of lf nu between group 1 and group 2 individuals.

nu

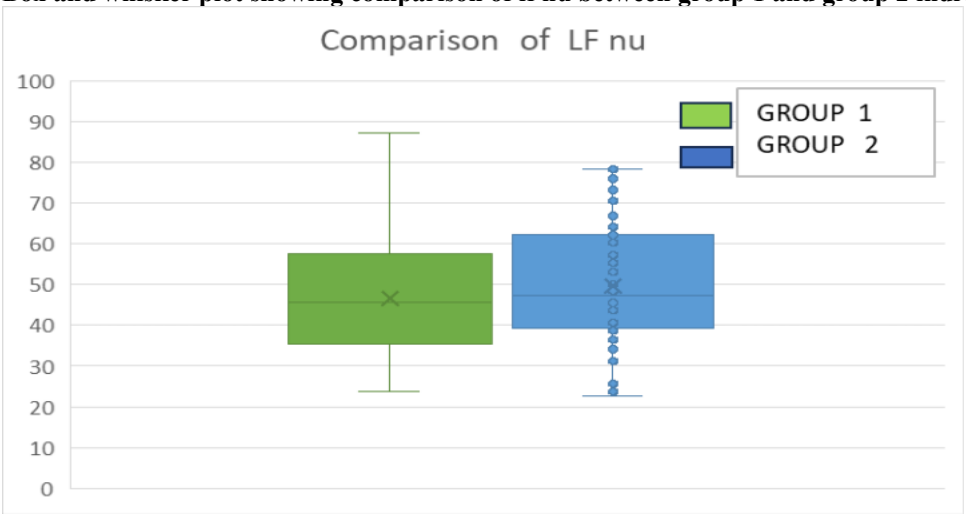


FIGURE NO 16: Box and whisker plot showing comparison of HF nu between group 1 and group 2 individuals.

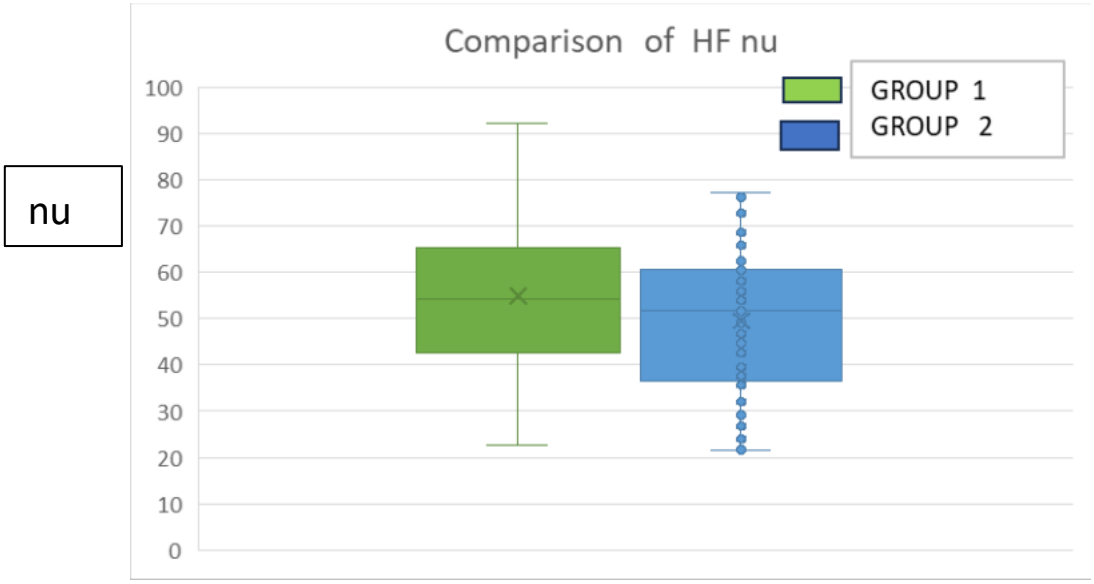
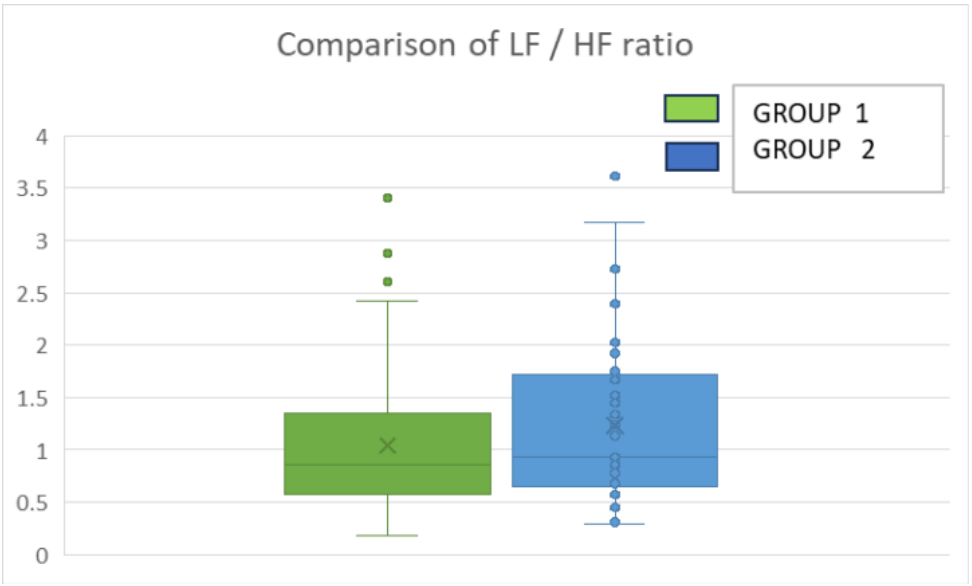


FIGURE NO . 17 : Box and whisker plot showing comparison of LF /HF ratio between group 1 and group 2 individuals.



OBSERVATION : Box and whisker plot showing no significant difference of frequency domain parameters between group 1 and group 2 individuals.
Risk of developing low HRV in Group 2 compared to Group 1:

The 75 th quartile of SDNN is 52.6 and the 75 th quartile of RMSS is 56.05 Number of people with SDNN lower than 52.6 in Group-1 is 32 and Group-2 is 43.
Number of people with RMSSD lower than 56.05 in Group-1 is 34 and Group-2 is 41.

The assumption is that SDNN and RMSSD values higher than 75 th quartile is having good autonomic reactivity.
Anything lower than 75 th quartile of SDNN Value 52. 6 is considered as low SDNN and higher than 52.6 is considered as high SDNN.

Anything lower than 75 th quartile of RMSSD Value 56.05 is considered as low RMSSD and higher than 56.05 is considered as high RMSSD .

TABLE NO. 8: Frequency distribution of high SDNN and RMSSD between Group 1 and Group 2 individuals.

	SDNN HIGH	SDNN LOW	RMSSD HIGH	RMSSD LOW

GROUP -1	18	32	16	34
GROUP-2	7	43	9	41

The risk of low HRV paramerters in Group 2 as defined by risk ratio is calculated and found to be :
The Risk ratio calculated for low SDNN will be 43/32 = 1.34.

The Risk ratio calculated for low RMSSD will be 41/34 = 1.20

The odds of having low SDNN in group - 2 can be calculated from the same table no: 23.
ODDS RATIO for low SDNN = Odds in group - 2 / Odds in group – 1= 0.289

The odds of having low RMSSD in group - 2 can be calculated from the same table no : 23.

ODDS RATIO for low RMSSD = Odds in group - 2 / Odds in group – 1 = 0.466

TABLE NO . 9 : Odds ratio analysis of low SDNN and Low RMSSD.

	ODDS RATIO (ln)	**CI (LOWER , UPPER)**	**P-VALUE**
SDNN	0.964	(- 0.068 , - 0.006)	0.021 *
RMSSD	0.976	(- 0.049, 0)	0.046 *

OBSERVATION : Odds ofhaving low SDNN and low RMSSD is higher in Group 2 than Group 1 indicating poor HRV in Group 2 individuals.

DISCUSSION
EXPLANATION OF THE RESULTS :
The resting short term analysis of HRV shows the following results .
The SBP was significantly increased in the Group-1 (control) than Group-2 (study) which is unusual with respect to the patho physiology of Covid-19. Hence, it could be an incidental finding.

COVID - 19 is found to increase sympathetic stimulation. Sympathetic stimulation increases BP by; 1) Vasoconstriction of resistance vessels 2) Venoconstriction (Increases venous return) 3) Cardiac stimulation (Increases heart rate and myocardial contractility) 4) Increased secretion of catecholamine from adrenal medulla 6.

The DBP was significantly increased in the Group-1 than Group - 2.
The MAP was significantly increased in the Group-1 than Group - 2.MAP is a average pressure recorded during the cardiac cycle. It is influenced by the cardiac output and systemic vascular resistance .

Autonomic nervous system plays an important role in regulating MAP .When MAP is increased , there is increased baroreceptor stimulation, the Nucleus tractus sollitarius decreases the sympathetic output and ultimately the result is a subsequent decrease in MAP.

Another study aimed to assess Ambulatory BP and BP variability in young population of 2 groups . Group 1 has 28 participants who had covid -19 before 11 weeks and Group 2 has 10 controls , ambulatory daytime , night time and 24 hour SBP,DBP and MAP were measured and found out that there is no significant difference between control and study group. This study also suggest that Covid -19 only exerts only shorter effects on BP in young adults 7 One more study did a cross sectional study comprising of two groups . Group 1 (participants who had SARS - COV infection before 6 months and non hospitalized) and Group 2 (Age and gender matched healthy controls).Cardiovascular risk factors , physical functioning and arterial stiffness were assessed for two groups. Cardiovascu lar risk factor was estimated by BP, Cardiac troponin I and CRP , Cardio femoral pulse wave velocity was used to measure arterial stiffness. Hand grip strength , gait speed ,accelerometry and questionnaire on fatigue was evaluated for assessing physical functioning .Study finding concluded that there is no significant difference in CV risk factors, CV biomarkers and arterial stiffness between two groups 9.

A cohort study, with two group - Group 1 had no history of COVID - 19 infection and posted for painless gastrointestinal endoscopy . Group 2 had history of COVID - 19 infection and posted for same procedure .SBP , DBP ,MAP were recorded before and after induction and observed that there is blood pressure variability in DBP and MAP in the Group -2 . This clearly indicates the impact of COVID 19 on cardiovascular changes . These findings were contradicted to our study 11.

In our study , we have not measured BP prior to the Covid infection 12 .

Regular cardio vascular parameters may not be able to pick up initial variations in the sympathovagal balance like HRV which has higher sensitivity.13

Time domain parameters like SDNN, RMSSD were lower in study group than control group which means a withdrawal of parasympathetic system . There is a significant change in Time domain parameters like RMSSD and SDNN in long C O V I D clinical group. 1 3

Ertugrul kurtoglu et al .,2021 ,conducted a study in a COVID -19 recovered individuals and evaluates cardiac autonomic function using HRV and found out that Time domain parameters like SDNN , RMSSD were all decreased in the study group than control group 14-15

Another study conducted by Hani Taman et al ,2023,did HRV analysis in myocardial injured covid 19 patients and Non myocardial injured covid 19 patients and found that Time domain parameters like SDNN and RMSSD were significantly reduced in myocardial injured covid 19 patients . This study also proves that HRV as a prognostic tool for diagnosing covid -19 induced cardiac dysautonomia. Our study shows similar finding but the study participants does not have any history of any myocardial injury16 .

Indian study conducted by Bhushan Shah et al. , 2022, to determine the prevalence of cardiac dysautonomia using AI model of HRV in 92 Covid -19 recovered individuals and 120 healthy volunteers and witnessed that one of the Time Domain Parameter (RMSSD) was significantly lower in the post covid -19 patients than healthy controls. This study is showing similar findings as that of our study 17 .

Another Indian study conducted by Senthamizhsevan et al ., in 2024. It was an analytical and observational study in male population of age range (30 to 70 years) and compared the autonomic reactivity using 5 minute lead - II HRV in study group who were in the period of 3 - 6 months following recovery from covid -19(n= 21) with age matched healthy control group(n= 21). Results estimated showing Frequency domain HRV Indices of LF Power , HF Power and Total Power were significantly reduced in the Covid -19 recovery group than control group which proves that there is depressed cardiac autonomic modulation in the study group. In our study , none of the frequency domain measures were found to be statistically significant 1 8 .

Adang et al , 2023 did a retrospective cohort study in the hospital of Netherland. This study was conducted in a 171 patients who got admitted in hospital for Covid - 19 infection between February and December 2020 .The aim of their study was to look for association between HRV recorded during admission and Pulmonary Function Test (PFT) recorded beyond 3 months after covid– 19 infection.Multinomial logistic regression model was performed for analysis. Their sample size was not sufficient to show Odds ratio closer to 1.00 than 0.63. Their result showed that there is no association between HRV and impaired pulmonary function after 3 months of Covid -19 infection . In our study , Odds ratio calculated for lower SDNN is 0.289 and for low RMSSD is 0.466. Odds of having low SDNN and RMSSD is higher in group - 2 than group - 1 individuals
19.

STRENGTH OF THE STUDY :
GROUP 2 (N= 50) who were RT PCR positive for Covid -19. RT-PCR is a validated tool approved by ICMR [53].The study population comprising of young adults (18 - 30 years) which is a unidentified population and they are gender matched. The early detection of cardiac dysautonomia can help the young individuals to modify their life style and seek advise from Health care Experts 2 0 .

LIMITATIONS : Covid Negative state was not tested in Group - 1.Some study participants may be infected with Covid - 19 virus and remain asymptomatic and untested. This may lead to grouping error. Multiple new strains of Covid - 19 have emerged during Covid pandemic. For e.x) Alpha (B.1.1.7) ,(B.1.351),Gamma (P.1) , Delta (B.1.617.2) and Omicron (B.1.1.529). Each Covid strain has different virulence and transmissibility rate [55]. But , this was not compared in the present study. Most of the participants got Covid -19 infection after getting vaccinated against COVID -19. Since COVID -19 vaccine has cardioprotective role, severity of Long Covid on cardiac autonomic function might be different from unvaccinated population .This was not compared in the present study. Follow up was not done for study participants with reduced HRV, in order to determine the persistence of altered autonomic function in these population .

FUTURE IMPLICATIONS :
This study can be further elaborated as a Basic Science Research (ex , Cell culture and Animal models) . Animal model can be done by inducing Covid -19 virus in them and the pathophysiology of Long COVID 19 can be studied.. In Cell Culture, the levels of cytokines and neurotransmitters modifications due to COVID - 19 can be studied. This study can be expanded in clinical set up and laboratories.(ex, Screening the Out patient department with H/O COVID - 19 infection in the past and testing them with biochemical and pathological tests). Clinicians can watch out for Long covid symptoms like fatigue, anxiety, insomnia and rule out other causes in young population and advice them for Life style modification.

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