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CARDIOVASCULAR MANIFESTATIONS IN POST-COVID PATIENTS – AN OBSERVATIONAL STUDY

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ABSTRACT

The COVID-19 pandemic has had a significant impact on global health & economy. The consequences of Covid persisting or manifesting beyond the acute phase or 'Post-COVID 19 conditions' affect multiple organ systems including pulmonary, cardiovascular, musculoskeletal and nervous systems. The pathophysiological mechanisms postulated include chronic inflammation,dysregulated autoimmune response and endothelial dysfunction. A hospital based observational descriptive study was conducted at Government TD Medical College Alappuzha to identify the clinical profile of post-COVID patients who presented with new onset cardiovascular symptoms. By convenience sampling, data from 100 patients were collected in semi-structured proformas during the one year study period, focusing on the sociodemographic profile, comorbidities, severity of COVID-19 infection, time since infection, vaccination status and the nature of new onset cardiovascular manifestations.61 of the 100 patients were males.55% were in the 46-65 age group.69% had a history of mild category of COVID-19 infection,15% moderate and 16% severe.57% had presented wthin 6 months of Covid.The most common symptoms were chest pain,breathlessness,palpitations,fatigue,pedal edema and pre-syncopal episodes.78 patients had MACE,of which 20 presented with cardiac failure. 60 patients were diagnosed with acute coronary syndrome,4 with other arterial thromboses, 6 with non-ischemic cardiomyopathy,2 with myocarditis/myopericarditis and 7 with venous thromboembolism.35 patients had some form of arrhythmia. The new onset cardiovascular events including MACE could be a sequelae of COVID-19 infection and hence post-COVID patients should be followed up with a focus on cardiovascular risk assessment, and measures for secondary prevention can be taken.

KEYWORDS: COVID19, POST-COVID, CARDIOVASCULAR, MACE

1. INTRODUCTION

COVID -19 is an infectious disease that was initially identified when a cluster of pneumonia cases was reported in Wuhan, China in December 2019. The disease rapidly spread within and outside China and was declared a Public Health Emergency of International Concern by the WHO on 30 January 2020.

The clinical spectrum of the disease varies in severity from mild to critical and can have varied respiratory and other systemic manifestations. Acute and long-term cardiovascular implications are known to occur in infections with Coronaviruses, including the Severe Acute Respiratory Syndrome

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(SARS) virus, the Middle East Respiratory Syndrome virus(MERS), the H1N1 influenza virus which caused the influenza epidemics in the recent past.(1)

The long-term morbidity associated with COVID-19 is equally worrisome as the mortality and morbidity associated with the acute phase of the disease. As the consequences of the illness began to take a toll on mankind worldwide, it became an epidemic of its own and has been referred to by various terms like 'post-COVID-19 condition', 'long COVID', and 'long-haul COVID'.(2) Since a standardized clinical case definition was lacking, WHO proposed a globally standardized working clinical case definition for Post-Covid-19 condition by a Delphi consensus which was defined as new onset or persisting symptoms occurring in individuals with a history of confirmed or probable COVID-19 infection, usually beyond 3 months from the onset of COVID-19 illness, and last for at least 2 months and cannot be explained by an alternate diagnosis. These symptoms may fluctuate or relapse over time.(2)

The Delphi consensus was not available at the time of protocol development for this study, and for the purpose of this study, post-COVID patients are defined as patients who had RT-PCR/ TRUENAT or rapid antigen test confirmed COVID-19 infection, and are clinically recovered from the acute phase of 25 COVID-19 infection (who are 21 days past symptom onset + improvement in symptoms+ resolution of fever for 72 hours without fever reducing medicine). This definition was adapted from an ongoing cohort study titled 'Long-term Impact of Infection With Novel Coronavirus (LIINC): An Observational Study' in the United States.(3)

The term 'Post-COVID-19 conditions' spans a wide range of symptoms and can involve multiple organ systems, including pulmonary, cardiovascular, musculoskeletal, and nervous systems, and psychological effects. The common symptoms include fatigue, breathlessness, post-exertional malaise, palpitations, chest pain, brain fog, headache, nausea, vomiting, anxiety, depression, skin rashes, and joint pain.(4) The most commonly reported cardiovascular symptoms include chest pain, palpitations, dyspnoea on exertion, pre-syncope, fatigue, shortness of breath, and lower extremity edema. (5)The pathophysiology of acute and chronic cardiovascular complications of covid-19 appears to be to be multifactorial,(6) and includes: the direct cardiotoxicity by the virus – SARS-CoV-2 downregulates ACE-2 expression;(7) hyperinflammation and cytokine storm – resulting in vascular and myocardial inflammation, plaque instability, and hypercoagulability; autoantibodies to cardiac tissue or anti-heart antibodies by molecular mimicry; systemic complications of COVID-19 like sepsis leading to cardiac injury and possibly as a consequence of the use of drugs like hydroxychloroquine, azithromycin, antivirals,(8) and steroids.

Being a newer disease of global impact, our understanding of the pathophysiology and sequelae of COVID-19 is still evolving. Research is ongoing worldwide to understand the acute and long-term impacts of this new pandemic, and to find out better preventive and treatment strategies.

2. METHODS

2.1 Objective : To study the profile of post-COVID patients presenting with new onset cardiovascular manifestations.

2.2 Type of Study: A hospital based observational study conducted at a tertiary care centre.

2.3 Study Population: The study was conducted among the post-COVID patients who presented with new onset cardiovascular symptoms at the OPD/casualty at our institution, a tertiary care centre in the state of Kerala over a period of one year from April 2021 to March 2022.

2.4 Sampling Method: Convenience sampling

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2.5 Sample Size Estimation : As similar studies were not available at the time of protocol development, the sample size was calculated using the formula 4PQ/D2, where P= prevalence was considered to be 50%, Q is (1-P) and D= absolute precision = 20% of prevalence; the estimated sample size was 100.

2.6 Inclusion Criteria-

Post-COVID patients - patients who had RT-PCR/ TRUENAT or rapid antigen test confirmed COVID-19 infection, and are clinically recovered from the acute phase of 25 COVID-19 infection (who are 21 days past symptom onset + improvement in symptoms+ resolution of fever for 72 hours without fever reducing medicine).

Since the Delphi consensus definition by WHO was not available at the time, this definition of post-COVID patients for the purpose of this study was adapted from an ongoing cohort study 'Long-term Impact of Infection With Novel Coronavirus (LIINC): An Observational Study' in the United States.(3)

2.7 Exclusion Criteria

• Patients with documented cardiac disease- myocardial disease, arrhythmias, cardiac failure, or thromboembolic phenomena.

• Patients less than 18 years of age.

2.8 Study Variables: Sociodemographic variables like age and gender, and clinical variables like cardiovascular symptoms, comorbidities, clinical severity and treatment of COVID-19 infection, time interval since infection, COVID-19 vaccination status.

2.9 Data Collection and Analysis: A total of 100 patients were selected after obtaining written informed consent. Data were collected from by direct questionnaire method, clinical examination and relevant investigations using a semi-structured proforma. Collected data were entered into MS Excel spreadsheet and analyzed using IBM SPSS software version 23.0. Qualitative variables were expressed as proportions and percentages.

2.10 The study was approved by the Institutional Review Board and the Institutional Ethics Committee.

3. RESULTS

3.1 AGE DISTRIBUTION

Age in Years	Frequency	Percent
18-45	31	31
46-65	55	55
66-85	14	14
Total	100	100

3.2 GENDER DISTRIBUTION

Sex	Frequency	Percent
Male	61	61
Female	39	39
Total	100	100

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3.3 CARDIOVASCULAR SYMPTOMS

SYMPTOM	Yes	
	Frequency	Percent
Chest pain	64	64
Dyspnoea	50	50
Palpitation	32	32
Pre-syncope	15	15
Fatigue	21	21
Pedal edema	19	19

3.4 CARDIOVASCULAR EVENTS

CARDIOVASCULAR EVENTS		Frequency	Percent
Acute Coronary Syndrome	No	40	40
	Unstable angina	19	19
	NSTEMI	15	15
	STEMI	26	26
Other arterial thromboses	No	96	96
	Limb ischemia	3	3
	Aorta and its branches	1	1
Arrhythmia	None (sinus rhythm)	65	65
	Sinus bradycardia	4	4
	Sinus tachycardia	15	15
	Atrial flutter	3	3
	AF	5	5
	AVRT/AVNRT	3	3
	VF/VT	3	3
	2nd degree/complete heart block	2	2
Non-ischemic cardiomyopathy	No	94	94
	Yes	6	6

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Myocarditis	No	98	98
	Yes	2	2
Venous thromboembolism	None	93	93
	DVT	3	3
	Pulmonary embolism	4	4

3.5 MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

MACE	**Frequency**	**Percent**
None	22	22
Acute MI	34	34
Cardiovascular death	1	1
Unstable angina	19	19
Heart failure	17	17
Acute MI + heart failure	5	5
Acute MI + heart failure+ cardiovascular death	2	2

3.6 DETAILS OF PAST COVID19 INFECTION

3.6.1 **Government of Kerala (DHS) Clinical Severity Category of COVID19 Infection**

GoK(DHS) disease category	**Frequency**	**Percent**
Cat A	39	39
Cat B	32	32
Cat C	29	29
Total	100	100

3.6.2 **WHO Clinical severity Category of COVID19 Infection**

Severity Category- WHO	**Frequency**	**Percent**
Mild	69	69
Moderate	15	15
Severe	16	16
Total	100	100

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3.6.3 Time Interval Since COVID-19 Infection

Time Interval Since COVID-19 Infection	Frequency	Percent
<6 months	57	57
6 months - 1 year	37	37
>1 year	6	6
Total	100	100

3.6.4 COVID-19 Treatment History

COVID-19 TREATMENT HISTORY		Frequency	Percent
Oxygen therapy and ventilaton	None	73	73
	O2 mask	14	14
	HFNC	5	5
	NIV	8	8
Antiviral	None	78	78
	Favipiravir	5	5
	Remedesivir	17	17
Antibiotics	None	45	45
	Azithromycin	33	33
	Cephalosporins	16	16
	Both	6	6
Steroids	No	73	73
	<7days	22	22
	>7 days	5	5
Anticoagulation	No	74	74
	Oral anticoagulation	1	1
	Parenteral (heparin)	25	25
Tocilizumab	No	96	96
	Yes	3	3

3.6.5 COVID-19 Vaccination Status

Type of Vaccine	Frequency	Percent
Details not Available	9	9

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Covishield	30	30
Co-vaccine	13	13
Total	52	52

3.6.6 Comorbidities

57% of the patients had one or more comorbidities.

COMORBIDITIES	Yes		No	
	Frequency	Percent	Frequency	Percent
Diabetes mellitus	17	17	83	83
Hypertension	25	25	75	75
Dyslipidemia	12	12	88	88
Thyroid disease	2	2	98	98
CVA	1	1	99	99
Kidney disease	2	2	98	98
COPD	4	4	96	96

3.6.7 Smoking and Alcohol use

ADDICTIONS	Yes		No	
	Frequency	Percent	Frequency	Percent
Smoking	19	19	81	81
Alcohol	7	7	93	93

4.DISCUSSION

4.1 DISCUSSION AND REVIEW OF LITERATURE

A hospital-based observational descriptive study was conducted at a tertiary care centre in Kerala, at a government medical college, to identify the clinical profile of post-COVID patients who presented with new onset cardiovascular symptoms. By convenience sampling, data from 100 patients were collected during the one-year study period, focusing on the age and gender profiles, comorbidities, clinical severity and management of COVID-19 infection, time interval since COVID-19 infection, vaccination status and the nature of new-onset cardiovascular manifestations.

4.1.1Age and gender distribution

We found that out of the 100, 31% of the post-COVID patients who presented with cardiovascular manifestations were in the 18-45 years age group, 55% were in the 46-65 years age group and 14% were in the 66-85 years age group.

A retrospective cohort study by *Ayoubkhani et al* reports that patients who were discharged after COVID-19 had increased rates of multiorgan dysfunction when compared with the expected risk in the general population. Patients with a history of COVID-19 infection had major adverse cardiovascular events 3 times more frequently after discharge from the hospital 3.0 (2.7 to 3.2) than in the matched

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control group. In this study, younger patients were found to have a higher relative risk for multi-organ dysfunction than those who were 70 years or older.(9)

In our study,61% of the 100 patients who presented with cardiovascular manifestations were males and 39% were females. This is in contrast with the findings from a review by Raman et al in which female sex and higher age were reported to be risk factors for long-COVID. (4) A large cohort study including non-hospitalized COVID-19 patients in the UK by Subramanian et al found that the risk for long COVID was increased in the female sex and that the risk appeared to increase with decreasing age. (10)

These studies have shown that while a higher proportion of men are found to have severe COVID-19 illness, long-term sequelae have shown some female predilection .This could probably be explained by the stronger innate and adaptive immune response to viral infection and faster viral clearance reported in women. This enhanced immune response probably makes women more prone to develop post-COVID sequelae which are proposed to have immunological and inflammatory pathophysiology.(10)

The difference found in the gender distribution could be due to the difference in methodology and the lower sample size. This was a descriptive study among 100 patients who were selected by convenience sampling.

4.1.2 **Cardiovascular symptoms and events**

Out of the 100 patients in our study, 64% of the patients had presented with chest pain. The other common symptoms were breathlessness (50%), palpitations(32%), fatigue (21%), pedal oedema(19%) and pre-syncopal episodes(15%).

A study by Huang *et al.* of 1733 patients who were hospitalized with COVID-19 in Wuhan, China, showed that 63% of post-COVID patients reported fatigue, 26% experienced breathlessness, and 5–9% had chest pain and palpitations at 6 months post-infection. At 12 months, 20% had fatigue while 30% reported breathlessness and 7% had chest pain.(11)

In another multicentre follow-up study by Evans *et al.* in 1077 patients who were hospitalized with COVID-19 in the UK showed that 48% had persistent fatigue, 41% had dyspnoea, and 21–28% had chest pain and palpitations at a median of 5 months after discharge.(12)

In our study, 60% of the patients had presented with acute coronary syndrome, of which 19% had unstable angina, 15% had non-ST elevation myocardial infarction and 26 % had ST-elevation myocardial infarction. One patient had presented with extensive arterial thrombosis in the abdominal aorta, renal artery, and femoral artery, while 3 patients had presented with acute limb ischemia due to peripheral arterial thrombosis. Three (3%) patients had presented with deep vein thrombosis while four (4%) had presented with pulmonary embolism.6 post-COVID patients had presented with non-ischemic cardiomyopathy which could not be attributed to other causes. Two had presented with myocarditis.45 % of the patients had presented with some form of arrhythmia of which 15% had sinus tachycardia, 4% had presented with sinus bradycardia, 3 (3%) had atrial flutter, 5(5%) had atrial fibrillation and one 3% had presented with AVRT /AVNRT. 3% had presented with ventricular arrhythmias, ventricular tachycardia, or ventricular fibrillation.2% had presented with high-degree heart block (AV block).

Inappropriate sinus tachycardia in post-COVID patients has been described in literature, with some centres reporting as much as 25-50% reporting with tachycardia or palpitations persisting beyond 12 weeks.(13)

78% of the 100 patients in our study had presented with major adverse cardiac events (MACE), of which 34% had presented with acute myocardial infarction, and 19% with unstable angina. 20 % had

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presented with cardiac failure.3 had died from cardiovascular events.13% had presented with cardiogenic shock.

A review published by Raman et al in the European Heart Journal reports that cardiovascular abnormalities myocardial inflammation, myocardial infarction, right ventricular dysfunction, and arrhythmias are being reported in patients beyond the acute phase.(4)

In a large study including 5.8 million US veterans, Xie et al reported that there was an increased incidence of cardiovascular events at one year in participants with a history of COVID-19 infection. The excess cardiovascular events when compared to matched controls included dysrhythmias(atrial fibrillation, atrial flutter, sinus tachycardia, sinus bradycardia, and ventricular arrhythmias), inflammatory heart diseases including pericarditis and myocarditis, ischemic heart diseases (myocardial infarction, ischemic cardiomyopathy, and angina), heart failure, non-ischemic cardiomyopathy, cardiac arrest, cardiogenic shock; thrombotic disorders including pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis.(14)

In a study by Ingul et al including 204 post-COVID patients at 3 months after discharge,27% were found to have dysrhythmias, including premature ventricular contractions in 18%, non-sustained ventricular tachycardia (NSVT) in 5%, atrial fibrillation/flutter in 4%, supraventricular tachycardia in 2% and sinoatrial block >3 seconds in 1 patient.(15)

4.1.3 **Clinical History of COVID-19 infection**

We found that of the 100 patients who had presented with cardiovascular symptoms, 39 had Government of Kerala Directorate of Health Services (DHS) clinical severity category-A COVID-19 infection, 32% had category B disease while 29% had category C disease.69% of the patients had mild COVID-19 infection according to the WHO category of COVID-19 clinical severity, while 15% had moderate disease and 16% had severe disease.

Studies have suggested that post-COVID sequelae may develop regardless of the severity of the acute phase of COVID-19 infection.(16) According to another cross-sectional study on Long-COVID, there was no significant difference in the incidence of long-term sequelae in patients who were admitted to intensive care units (ICU) and the patients who were managed in wards.(17) An observational study by Dennis et al found that patients with mild symptoms during COVID-19 infection also develop long-term symptoms.(18)

We found that 57% of the patients who presented with cardiovascular manifestations had been infected with COVID-19 within the past 6 months, 37% had presented between 6 months and 1 year of COVID-19 infection and 6% had presented after 1 year of COVID-19 infection.

27% of the patients who presented with cardiovascular manifestations had received some form of oxygen therapy during the acute phase of COVID-19.8 patients (8%) had received non-invasive ventilation. None of the participants had received invasive ventilation. A study by Mandal et al among 384 patients who were discharged after hospitalization for COVID-19 found that patients treated with oxygen alone, or with continuous positive airway pressure, or with invasive ventilation had comparable outcomes.(17)

17% of the post-COVID patients in our study had received treatment with remedesivir during the acute phase of COVID-19 illness while 5% had received favipiravir. 3% had received tocilizumab.33% had received treatment with azithromycin, 16 % had been treated with cephalosporins when they were infected with COVID-19, while 6% had received both.27% of the patients had received steroids as part of their COVID-19 treatment, of which 22% had been given steroids less than a week while 5 percent had

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received steroids for one week or more.26% had received anticoagulation when they were being treated for Covid.

The impact of drugs and treatment modalities used to treat the acute phase of COVID-19 illness on long-term cardiovascular risk health is still unclear. Currently, the most widely used treatment options include anti-inflammatory drugs such as dexamethasone and monoclonal antibodies such as tocilizumab, an IL-6 receptor antagonist, and antivirals such as remedesivir and favipiravir. A multiplatform adaptive randomized controlled clinical trial by Lawler et al reported a beneficial role in survival until hospital discharge with therapeutic dose heparin in moderately ill patients, but this benefit was not found during critical illness.(19)

Other studies such as ACTION,(20) INSPIRATION, (21) and RAPID(22) trials reported no difference in primary outcome measures among patients with therapeutic and prophylactic dose anticoagulation. Azithromycin is known to prolong the QT interval and has the potential to cause arrhythmias, but its implications in post-COVID syndrome are not known.(23)

A prospective study by Boglione et al including 449 patients hospitalized with COVID-19 suggested that treatment with remdesivir led to a 35.9% reduction in the rate of development of long-COVID syndrome in follow-up.(24)

Covid vaccination

Out of the 100 patients, 52% had received COVID vaccination. 36 % had received 2 doses of the vaccine while 16 % had received a single dose. Details of COVID vaccination were available for 43% of patients, of which 30% had received Covishield and 13% had received Co-vaccine.

A large meta-analysis of RCTs has suggested that influenza vaccination could lower the risk of major adverse cardiovascular events. (25)

An international survey by Strain et al suggested that COVID-19 vaccination may improve long COVID symptoms.(26) It has been postulated that this improvement in symptoms might be explained by accelerated clearance of the virus and a reduced chronic inflammatory response following vaccination.(27)There have been reports of vaccine-induced adverse cardiovascular outcomes, which were rare, including myocarditis, cardiomyopathy, vaccine-induced prothrombotic immune thrombocytopenia (VITT), (28) and increased incidence of acute ischemic events.(29)

4.1.4 **Co-morbidities and addictions**

57% of the patients had one or more co-morbidities while 43% had none. 25% of the patients had a history of systemic hypertension, 17% had diabetes mellitus, 12% had a history of dyslipidemia, 4% had COPD, 2% had thyroid disease, 2% had kidney disease, while one had ischemic cerebrovascular accident.58% of the 100 patients who presented with cardiovascular manifestations had body mass index (BMI) in the normal range, 22% were overweight, 17% were obese and 3% were underweight. 19% of the patients were smokers while 7% gave a history of alcohol use.

A prospective cohort study by Perez et al among 277 post-COVID patients found that no baseline clinical characteristics like gender, hypertension, diabetes, obesity, cardiovascular disease, chronic respiratory disease, or severity of acute COVID-19 infection had a bearing on the development of post-COVID syndrome.(23)

Another study by Sudre et al among 4182 patients found that participants' attributes like increasing age, female sex, and increased body mass index had a higher risk of developing post-COVID symptoms.(30)

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A large cohort study by Subramanian et al concluded that risk factors for the development long COVID included female sex, socioeconomic deprivation, smoking, obesity, and the presence of comorbidities.(10)

The results from various studies are conflicting, which could be due to the differences in methodology, selection criteria, and sample size.

4.2 CONCLUSIONS

This was an observational study conducted at a tertiary care centre in Kerala among 100 post-COVID patients who presented with cardiovascular manifestations. A majority (61%) of the patients in the study population were males, and 86% of the patients were younger than 66 years. The major cardiovascular symptoms in post-COVID patients were chest pain (60%), breathlessness (50%), palpitations (32) %, fatigue (21%), pedal edema (19%) and pre-syncopal episodes (15%). 78% of the 100 patients in the study had presented with major adverse cardiac events (MACE), of which 34% had presented with acute myocardial infarction, 19% with unstable angina.20 % had presented with cardiac failure. The other major cardiovascular presentations were arrhythmias, non-ischemic cardiomyopathy, myocarditis, and venous and arterial thromboembolic events. The majority of patients who presented with cardiovascular events have had a non-severe COVID-19 infection (WHO clinical categorization), and most patients (57%) had presented with new onset cardiovascular symptoms within 6 months of COVID-19 infection.

4.3 RELEVANCE OF THE STUDY

COVID-19 has had an impact on every aspect of human life globally, with its acute and long-term complications causing morbidity and mortality, having a significant impact on quality of life, hindering economic growth, and straining health resources worldwide.(31)

Persistent or new onset symptoms occurring beyond the acute phase of COVID-19 infection or the long-term sequelae have been reported from around the globe, with some studies reporting that as much as 90% of COVID-19 survivors develop some kind of sequelae, including general symptoms such as fatigue as well as severe multisystem manifestations.(32)

There is considerable variability in the prevalence of post-COVID sequelae reported from across the globe, which could be attributed to varying methodology, choice of controls, study design, varying criteria being used to define post-COVID19 or long-COVID, varying sources of enrolment in the study, and varying socio-demographic patterns and age groups, presence of c-morbidities and vaccination status.(4)

The disease is still evolving with the emergence of new variants, and so are the clinical manifestations, both acute and long-term. Research is ongoing worldwide to understand this novel pandemic better.

This is an observational study among post-COVID patients presenting with cardiovascular symptoms to a tertiary care centre in Kerala, a Southern Indian state, to understand the pattern of cardiovascular manifestations, and the clinical profile of patients with cardiovascular sequelae. An understanding of the cardiovascular sequelae in post-COVID patients can help in proper assessment and follow-up, which can help in reducing the mortality and morbidity associated with the sequelae.

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4.4 LIMITATIONS OF THE STUDY

The study was conducted among 100 patients with a history of COVID-19 infection, larger scale studies might be needed to determine the pattern and risk factors of post-COVID19 cardiovascular sequelae more precisely. Since this was a descriptive study, causal associations between comorbidities, age, gender, severity and management of COVID19 infection, and the long-term outcomes could not be established. Ours is a tertiary care centre which treats mostly referred cases, so there could be a referral bias where patients with minor symptoms might not have been included.

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