

# Cardiovascular Manifestations in Moderate-to-Severe COVID-19 Patients and their Correlation with Inflammatory Markers

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## Abstract

**Introduction:** SARS-COV-2 induced novel coronavirus disease (COVID-19) associated high morbidity and mortality was the most threatening medical challenge in this century. COVID-19 induces multiple cardiovascular complexities such as myocarditis, pericarditis, acute myocardial injury, cardiogenic shock, arrhythmias, cardiac arrest and subsequently heart failure. Early diagnosis could help to discern at-risk patients to facilitate early treatment.

**Aim:** To study the cardiovascular manifestations in moderate-to-severe COVID-19 patients and their correlation with inflammatory markers.

**Methods:** This was an observational study done in a tertiary care institute of Northern India in the state of Uttar Pradesh on moderate and severe COVID-19 patients. Detailed history and clinical examination were done along with laboratory work-up to look for cardiovascular involvement in patients with COVID-19 disease.

**Results and Conclusion:** Out of 100 cases, 54% were moderate and 46% were severe; 50% males and 50% females in severe group, most of them aged above 40 years with hypertension (50%) and diabetes (27%) as leading associated co-morbidities. Inflammatory markers like CRP, LDH and ferritin were significantly raised and correlated with the severity of the disease ( $p < 0.05$ ). ECG revealed sinus tachycardia (44%) as the most common finding. In echocardiography, the most common finding was LV diastolic dysfunction (30%), followed by LV systolic dysfunction (23%), RV systolic dysfunction (15%). Most common valvular abnormality was tricuspid regurgitation (38%) followed by mitral regurgitation (30%). Pulmonary artery hypertension (14%), pericardial effusion (6%) and regional wall motion abnormalities (8%) were also seen.

**Conclusion:** COVID-19 disease is associated with significant involvement of the cardiovascular system and is the second most common cause of mortality after respiratory system. Also, increased levels of inflammatory markers correlate with the severity of the disease.

## Introduction

The COVID-19 pandemic, caused by SARS-COV-2 virus had a crippling effect on global health. Emerging from Wuhan province in China, this virulent virus soon took almost every country in the globe under its grasp with 649,896,619 confirmed patients and 6,654,860 deaths reported as of Dec. 12, 2022<sup>1</sup>.

Patients infected with SARS-CoV-2 present with a spectrum of clinical severity varying from asymptomatic to fatal conditions. Immune system disturbance has been considered as one of the hallmarks of COVID-19, especially cytokine release syndrome, lymphopenia along with endothelial dysfunction via Angiotensin-Converting Enzyme 2-receptor (ACE-2) and myocardial damage<sup>2</sup>. Inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6 (IL-6), D-dimer and procalcitonin are drastically increased during

cytokine storm creating parenchymal lesions in vital organs. COVID-19 is a disease that involves multiple body systems of which manifestations of the cardiovascular system were the main concern in our study. These can be acute heart failure, ischaemic heart disease, acute myocarditis, arrhythmias, venous thromboembolism, and pericardial diseases.

The aim of the study was to study the cardiovascular manifestations in moderate-to-severe COVID-19 patients and their correlation with inflammatory markers.

## Material and Methods

This was an observational study conducted on 100 patients with moderate and severe COVID-19 disease admitted in the Medicine department of Sarojini Naidu Medical College, Agra during the period December 2020 to June 2022. Only patients >18 years of age were enrolled. All the 100 patients

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were subjected to detailed clinical examination and investigations: CBC, SGOT/SGPT, bilirubin, creatinine, urea, electrolytes, lipid profile, CRP, LDH, ferritin, troponin T, pro-BNP, chest X-ray postero-anterior view, electrocardiography and 2D echocardiography.

## Results

A total of 100 patients with moderate (54%) and severe (46%) COVID-19 formed the study population. All the clinical details, progress of disease, and outcome were recorded and following observations were made:-

### 1. Demographic features:

Age of patients included in the study varied from 18 to 83 years. The majority of patients belonged to age > 40 yrs (72%) and percentage of severe COVID-19 patients was more in the age group of > 60 yrs (34.78%).

**Table I: Age distribution.**

Age group (years)	Moderate COVID-19		Severe COVID-19		Total	
	No.	%	No.	%	No.	%
18-20	3	5.55	2	4.34	5	5.00
21-40	11	20.37	12	26.08	23	23.00
41-60	22	40.74	16	34.78	38	38.00
>60	18	33.33	16	34.78	34	34.00
Total	54	100.00	46	100.00	100	100.00
Mean ± SD	52.22 ± 18.0		51.28 ± 16.91			

The percentage of male and female genders was 58.18% and 40% in the moderate COVID-19, 50%, and 50% in the severe COVID-19 group.

**Table II: Comparison of gender frequencies between moderate and severe COVID-19 patients.**

Gender	Moderate (n = 54)		Severe (n = 46)	
	N	%	N	%
Male	32	59.25	23	50.00
Female	22	40.74	23	50.00

### 2. Associated comorbidities

In the present study, hypertension was the leading comorbidity for COVID-19 disease in 50%, followed by diabetes mellitus (27%), dyslipidaemia (20%), obesity (12%), chronic obstructive pulmonary disease (6%), asthma (4%), pulmonary tuberculosis (6%), chronic kidney disease (4%), carcinoma (2%) and other (14%) with no associated comorbidities.

**Table III: Distribution of patients according to comorbidity between moderate and severe COVID-19 patients.**

Comorbidity	Moderate COVID-19 (n = 54)		Severe COVID-19 (n = 46)		Chi sq.	p-Value	Total	
	N	%	N	%			N	%
Hypertension	20	37.03	30	65.21	6.804	<b>0.009</b>	50	50%
T2DM	9	16.66	18	39.13	5.213	<b>0.02</b>	27	27%
Dyslipidaemia	5	9.26	15	32.61	7.08	<b>0.008</b>	20	20%
Obesity	2	3.70	10	21.74	6.04	<b>0.014</b>	12	12%
COPD	2	3.70	4	8.60	181	0.178	6	6%
Asthma	1	1.85	3	6.52	162	0.11	4	4%
Pulmonary Tuberculosis	5	9.26	1	2.17	1.13	0.287	6	6%
CKD	2	3.70	2	4.35	0.03	0.870	4	4%
Carcinoma	2	3.70	0	0.00	0.36	0.547	2	2%
None	6	11.11	8	17.39	0.38	0.540	14	14%

### 3. Investigations

It was noted that the level of inflammatory markers viz. CRP, LDH, and ferritin was significantly higher in severe COVID-19 group patients and correlated with severity of the disease.

**Table IV: Mean values of inflammatory markers in moderate and severe COVID-19 patients.**

	Moderate COVID-19 (n = 54)		Severe COVID-19 (n = 46)		T	p-Value
	Mean	±SD	Mean	±SD		
CRP (mg/L)	36.56	46.35	100.6	40.60	-10.439	<b>0.002</b>
LDH (mg/dL)	376.29	220.83	1037.73	399.67	-6.399	<b>0.001</b>
Ferritin (ng/mL)	443.67	274.24	962.95	517.38	-3.169	<b>0.002</b>

Raised levels of Troponin T were seen in 20 patients of COVID-19, which included 15 severe patients and 5 moderate patients signifying cardiac injury. Pro-BNP levels were also significantly increased in 29 COVID-19 patients, of which 15 were severe and 14 were moderate.

**Table V: Cardiac biomarkers in moderate and severe COVID-19 patients.**

Troponin T (ng/mL)	Value	Moderate COVID-19	Severe COVID-19	Total
	0-14	37	15	52
	14-99	17	11	28
	>99	5	15	20
Pro-BNP (pg/mL)	<300	42	29	71
	>300	14	15	29

#### 4. Electrocardiography:

Sinus tachycardia was present in 44% of patients with ST-T changes in 10%. Right ventricular hypertrophy, right atrial enlargement, and right bundle branch block together constituted 18% whereas left ventricular hypertrophy, left atrial enlargement, and left bundle branch block constitute 13%. Atrial premature complexes and Ventricular premature complexes were present in 4% and 6%, respectively. Low voltage complexes were seen in 6%. Diffuse ST segment elevation with concavity upwards suggesting pericarditis was seen in 7%. Atrial fibrillation (6%) and atrial flutter (2%) were also seen. Changes representing Acute Coronary Syndrome were also noted in 4%. Ventricular tachycardia and complete heart block were also seen in 3% and 1% each, respectively. Normal electrocardiography was seen in 59% of patients.

**Table VI: Various electrocardiogram changes seen in patients.**

Electrocardiography findings	No. (%)
Sinus tachycardia	44%
LA enlargement	3%
RA enlargement	5%
APC	4%
VPC	6%
RVH	9%
LVH	8%
RBBB	4%
LBBB	2%
Complete heart block	1%
Wide QRS with A-V dissociation	3%
Atrial flutter	2%
AF	6%
ST elevation V1-V4	1%
ST elevation V1-V6	1%
ST elevation II, III, avF	1%
ST-T changes	10%
Diffuse ST elevation with concavity upwards	7%
Low voltage complexes	6%

#### 5. Echocardiographic abnormalities

Diastolic dysfunction (DD) of the left ventricle was the most common abnormality detected in echocardiography and accounted for 30% of total patients, in which 20% of the patients had grade 1 DD, 8% had grade 2 DD and 2% had grade 3 DD. LV systolic dysfunction was seen in 23% of patients. 4% patients had severely reduced ejection fraction (LVEF) (< 30%), 9% had moderately reduced LVEF (30% - 40%) and 10% had a mild reduction in LVEF (40% - 50%). RV

systolic dysfunction was seen in 15% of patients who had abnormal TAPSE scores of < 17 mm.

14% patients developed pulmonary artery hypertension in which 10% had PASP in the range of 30 - 50 mmHg whereas 4% had PASP in the range of 70 - 90 mmHg. Among valvular abnormalities, tricuspid regurgitation was seen in 38% of total patients followed by mitral regurgitation (30%), pulmonary regurgitation (12%) and aortic regurgitation (5%). Pericardial effusion (6%) and regional wall motion abnormalities (8%) were also seen.

**Table VII: Summary of findings on echocardiography in moderate and severe COVID-19 patients.**

Echocardiography findings	No. (%)
Normal	59%
LV Diastolic dysfunction	30%
LV Systolic dysfunction	23%
RV Systolic dysfunction	15%
Concentric LVH	10%
Regional wall motion abnormalities	8%
Pulmonary artery hypertension	14%
Mitral regurgitation	30%
Tricuspid regurgitation	38%
Pulmonary regurgitation	12%
Aortic regurgitation	5%
Pericardial effusion	6%

#### 6. Outcome of Moderate and Severe COVID-19 patients

The total number of patients who died were 32. Among them, 22 patients were severe COVID-19 patients and 10 patients were moderate COVID-19. The maximum number of patients who died were in the age group of  $\geq 60$  years which was 17 in number, 11 patients died in the age group 40 - 60 years followed by 4 patients who died in the age group 18 - 40 years. 18 patients were male and 14 were female. Among them, 25 patients had some form of cardiovascular involvement.

#### Discussion

The effect of COVID-19 disease on cardiovascular system is not fully understood currently. This study was undertaken to study the cardiovascular manifestations in moderate-to-severe COVID-19 patients. We enrolled 100 patients with moderate and severe COVID-19 disease admitted in Medicine Department of Sarojini Naidu Medical College, Agra. Hypertension and diabetes mellitus were the leading comorbidities in our study which was also noticed by Line Kabi<sup>3</sup> and Sumon Ganguli<sup>4</sup> in their study who also reported

that the most frequent comorbidities were hypertension (46%), and diabetes (40%).

In our study, the mean levels of inflammatory markers like CRP (100.6 mg/L), LDH (1037.73 mg/dL), and ferritin (962.95 ng/mL) with a p-value of 0.002, 0.001, and 0.002, respectively, were significantly higher in the severe COVID-19 group and correlated with the severity of the disease. Dysregulation of immune response by SARS-CoV-2 virus, when it invades the host is likely mediated by inflammatory cytokine storm, evidenced by an increase in the serum levels of LDH, ferritin, and CRP. This is consistent with the results of Huang, Wang, Lin *et al*<sup>5</sup>, who found LDH, CRP, and ferritin level was significantly elevated in COVID-19 patients, which required intensive care unit care compared to patients that did not require ICU care.

Raised levels of Troponin-T and Pro-BNP were seen in 20 and 29 patients of moderate and severe COVID-19, respectively. The mechanisms explaining myocardial injury in those with COVID-19 infection include direct (“non-coronary”) myocardial damage by ACE2 – the binding site for the SARS-CoV-2 – in cardiomyocytes, some have postulated that myocarditis might explain the rise of high-sensitivity cardiac Troponin in some patients. Lastly, acute myocardial infarction (MI) is always possible. Biomarkers of myocardial stress, i.e., natriuretic peptide is frequently elevated among patients with heart failure and are associated with an unfavorable course among patients with ARDS. Shahzad Khan<sup>6</sup> and Hahramani *et al*<sup>7</sup>, also concluded that increased levels of cardiac biomarkers correlates with the severity the disease and with worse outcomes.

In our electrocardiographic study, sinus tachycardia (44%) was the most frequent finding, followed by right side changes (18%), left-sided changes (10%), ACS (4%) along with rhythm abnormalities like AF, VT, etc. Our results were in accordance with a study by Brit Long<sup>8</sup> where the commonest ECG abnormality was sinus tachycardia followed by ST-T segment changes, atrial fibrillation, ventricular arrhythmias and QTc prolongation. They opined that ECG abnormalities may be due to cytokine storm, hypoxic injury, electrolyte abnormalities, plaque rupture, coronary spasm, microthrombi or direct endothelial or myocardial injury.

Left ventricular diastolic dysfunction (30%) was the most common abnormality detected in echocardiography followed by LV systolic dysfunction (23%) of patients, RV systolic dysfunction (15%) and 14% develop pulmonary artery hypertension. Among valvular abnormalities, TR (38%), MR (30%), PR (12%) and AR (5%) were seen. Regional wall motion abnormalities and pericardial effusion were seen in 8% and 6% of patients respectively. Marcelo Luiz Campos Vieira<sup>9</sup> found that echocardiography was

normal in 46% of patients, 31% had left ventricular diastolic dysfunction, 17.1% presented with right ventricular dysfunction, 18% with decreased left ventricle ejection fraction, 16.2% had abnormal left ventricle global longitudinal strain, and 28% had pericardial effusion.

A total of 32 patients died in our study – 22 of these patients were severe COVID-19 and 10 patients were moderate COVID-19. Male: female ratio was 18:14 predominantly in the age group of  $\geq 60$  years. It was staggering to note that 25 out of 32 mortalities had some form of cardiovascular involvement. 68 patients out of 100 improved and discharged from the hospital. Laura A Bienvenu *et al*<sup>10</sup> found that records from China, South Korea, Italy and Germany suggested that males accounted for 59 - 75% of COVID-19 deaths in comparison to females. Williamson EJ *et al*<sup>11</sup> found that older age is a classical cardiovascular disease risk factor and is most profoundly implicated in COVID-19 related deaths. Rishi K. Wadhwa<sup>12</sup> in his study concluded that there was an increase in deaths caused by ischaemic heart disease and hypertensive diseases in some regions of the United States during the initial phase of the COVID-19 pandemic. These findings suggest that the pandemic may have had an indirect toll on patients with cardiovascular disease.

## Conclusion and Summary

In our study, hypertension (50%) was the leading comorbidity with COVID-19 disease, followed by diabetes mellitus (27%), dyslipidaemia (20%), and were significantly associated with the severity of the disease. It was noted that the levels of inflammatory markers like CRP ( $p = 0.002$ ), LDH ( $p = 0.001$ ), and ferritin ( $p = 0.002$ ) were significantly higher and correlated with the severity of the disease. Levels of Troponin-T and Pro-BNP levels were also significantly increased in 20 patients and 29 COVID-19 patients, respectively signifying cardiac injury. In electrocardiography, sinus tachycardia (44%) was the most common finding with ST-T changes in 10%. RVH, RAE, and RBBB together constituted 18%, whereas LVH, LAE, and LBBB constituted 13%. Left ventricular diastolic dysfunction (30%) was the most common abnormality followed by LV systolic dysfunction (23%) and RV systolic dysfunction (15%). Fourteen per cent (14%) of the total patients developed pulmonary artery hypertension. Among valvular abnormalities TR (8%), MR (30%), PR (12%) and AR (5%) were seen. Pericardial effusion (6%) and regional wall motion abnormalities in (8%) were also seen. The total number of patients who died were 32. Among them, 25 patients had some form of cardiovascular involvement in moderate and severe COVID-19 patients.

In our study, cardiac dysfunction was seen in 35% patients of moderate and severe COVID-19 patients, which was

associated with high morbidity and mortality. Cardiac mortality was the second most common cause of death after respiratory failure in COVID-19 in our study. Thus, cardiac screening of all moderate and severe COVID-19 patients, especially, hypertensive, diabetics, and old age, and earlier treatment may reduce cardiac mortality and morbidity. The level of inflammatory markers CRP, LDH, and ferritin were significantly higher in the severe group. Inflammatory markers have a prognostic significance in patients with COVID-19 with higher levels being associated with worse outcomes so they could help to discern at-risk COVID-19 patients to facilitate early treatment.

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