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Echocardiographic Assessment of Pulmonary Hypertension in Moderate to Severe Post Covid-19 Patients

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Abstract

Background: Pulmonary Hypertension (PH) is one of the long term complications of COVID-19 disease. PH is associated with increased morbidity, by leading to progressive right heart failure.

Aim: The aim of this study was to determine, by means of transthoracic echocardiography, the incidence of PH in moderate to severe post-COVID-19 patients**.**

Design: In a study of 163 post-COVID-19 patients, only 100 patients completed follow up. These moderate or severe COVID-19 patients underwent a complete cardiologic and echocardiographic examination at 2 and 6 months of follow up after COVID-19 disease.

Methods: Their initial laboratory data was collected from the hospital records.The pulmonary artery systolic pressure was calculated using echocardiography, by adding Right Atrial Pressure to four times the square of peak Tricuspid Regurgitate velocity.

Results: We observed the incidence of PH in the study population was 29% at 2 months and 19% at 6 months of post-COVID-19 disease. Maximum no. of patients who were found to had PH at 2 and 6 months, belonged to severe COVID-19 disease and had received longer duration of oxygen therapy during COVID-19 illness. We observed that PH was seen comparatively more in older age patients, with raised d-dimer, CRP and ferritin levels, and were associated with co-morbidities like diabetes and hypertension.

Conclusion: We concluded that PH is a long term complication of COVID-19 disease and more the severity of COVID-19 disease, more are the chances of developing PH.

Keywords: COVID-19, Pulmonary hypertension, echocardiography, CRP, D-dimer, ferritin

Introduction

Coronavirus disease 2019 (COVID-19), the highly contagious viral illness, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had a catastrophic effect on the world's demographics and resulted in millions of deaths worldwide.[1] Many people with COVID-19 recovered completely, but many suffered from long-term effects of COVID-19 disease, like fatigue, joint pains, headache, cough, and shortness of breath. One of these long-term effects is pulmonary arterial hypertension and right ventricular failure.[2] The main mechanisms responsible for pulmonary hypertension are vascular remodelling and elevated pulmonary vascular resistance (PVR). Primary means of elevated PVR are sustained hypoxic pulmonary vasoconstriction, uncontrolled pulmonary vascular remodelling and thrombosis in

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situ.[3] Pulmonary Hypertension (PH) presents most commonly as breathlessness and other features include chest pain, syncope, fatigue.[4]Diagnosing and preventing PH is crucial as pulmonary arterial hypertension (PAH) is associated with significant morbidity and mortality in post-COVID-19 patients, as it can lead to progressive right-sided heart failure.[5]

Material and methods

A prospective observational study was conducted to evaluate the incidence of pulmonary hypertension in moderate and severe post-COVID-19 patients. These moderate and severe COVID-19 disease patients were recruited from the patients admitted to isolation wards of Rajindra Hospital Patiala, during time period of 2 years from 1st July 2020 to 30th June 2022. These patients were followed up in post-COVID-19 OPD at 2 and 6 months after COVID-19 disease.

During hospital admission, the COVID-19 cases were diagnosed with RTPCR (reverse transcriptase polymerase chain reaction) assay performed on nasopharyngeal swabs. The diagnosed cases of COVID-19 were categorized into moderate or severe COVID-19 disease on the basis of oxygen saturation, respiratory rate and other clinical features. In mild disease, SpO2 of patient is >94% on room air, in moderate disease SpO2 is 90-94% on room air or respiratory rate 24-30/min and in severe disease SpO2 is <90% on room air or respiratory rate >30/min.[6] 163 consecutive moderate to severe post-COVID-19 cases were taken up for the study after applying the specified inclusion and exclusion criteria. Figure 1 describes the study design. Inclusion Criteria: All moderate and severe post-COVID-19 patients who followed up in post-COVID-19 OPD and age >18 years. Exclusion Criteria: All previously diagnosed cases of PH and all asymptomatic and mild cases of COVID-19 disease.

These patients were followed up in post-COVID-19 OPD at 2 and 6 months after recovery from COVID-19 disease. Out of 163 patients, only 100 patients completed follow up and rest were lost to follow up. These 100 patients were analysed for signs of PH like palpable P2 in left 2nd intercostal space, palpable right ventricular heave, increased intensity of pulmonic component of second heart sound and tricuspid regurgitation murmur on auscultation.[7] These patients were subjected to ECG, Chest X-Ray and transthoracic 2D echocardiography and Doppler studies at 2 and 6 months of follow up. Reports of blood investigations like complete hemogram, serum CRP (C-reactive protein), d-dimer and serum ferritin were obtained from their hospital records.

Pulmonary arterial pressure was estimated with transthoracic echocardiography. PASP (Pulmonary Artery Systolic Pressure) is assumed to be equivalent to RVSP (Right Ventricular Systolic Pressure) provided pulmonary stenosis is absent. RVSP was calculated by adding RAP (Right Atrial Pressure) to four times the square of peak Tricuspid Regurgitate Velocity (TRV_{max}).[8] PASP was calculated by using transthoracic 2D echocardiography as follows:

$PASP = RVSP = 4(TRV_{max})^2 + RAP$

The value of PASP ≥35 mm Hg at rest, indicates PH, with the severity ranging from mild (35–50 mmHg), to moderate (50–70 mm Hg) and severe (>70 mm Hg).[9]

Observation and result

The present study was carried out among moderate and severe post-COVID-19 patients, who presented to Rajindra Hospital, Dept. of Medicine and completed follow up at 2 and 6 months of post-COVID-19 disease.

Table 1: Demographic and clinical profile of COVID-19 patients

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

Parameter		**n=100**
Age (in years)		50.37(mean)
Male:Female		57:43
Clinical Features	Fever	98
	Cough	88
	Breathlessness	100
	Sore throat	71
SpO2 (%)		88.53±8.81 (mean)
Respiratory Rate (per min)		29.01±5.70 (mean)
Severity of COVID-19	Moderate	24
	Severe	76
Mode of Oxygen	Face Mask	22
	Venturi	13
	NRM	44
	HFNC	6
	BiPAP	15
	Invasive Ventilation	0
Duration of oxygen (in days)		9.85±6.7(mean)
D-Dimer (mg/L)	<0.5	16
	0.5-1	41
	1-2	24
	2-4	11
	≥4	8
CRP (mg/L)	<6	4
	6-30	52
	30-50	24
	>50	20
Ferritin (ng/ml)	<200	25
	200-1000	64
	≥1000	11
Co-morbidity	HTN	34
	DM	39

Table 1 showed that out of 100 patients, the mean age was 50.37 years, and 57% of the patients were men. All the patients presented with breathlessness while majority of them had fever and cough. The mean respiratory rate on hospital admission was 29.01/min while mean SpO2 was 88.53%. We observed that 24% patients were having moderate COVID-19 and 76% patients were having severe COVID-19 disease. We found that 65% patients received oxygen on the high flow oxygen devices and the patients received oxygen for mean duration of 9.85 days. The majority of the patients (65%) had moderately raised d-dimer levels while 19% had severely raised d-dimer levels. Also, 96% of patients had raised CRP values of ≥6 mg/L and 75% of patients had raised ferritin values of >200 ng/mL. Out of 100 patients Diabetes (DM) was present in 39% patients while Hypertension (HTN) in 34% patients.

Table 2: Incidence of pulmonary hypertension in moderate to severe post-COVID-19 patients at 2 and 6 months

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

Severity of COVID-19	Pulmonary Hypertension at 2 Months		Pulmonary Hypertension at 6 Months	
	Present	Absent	Present	Absent
Moderate	2	22	1	23
Severe	27	49	18	58
Total	29	71	19	81
P value	0.010		0.038	
Significance	S		S	

Table 2 showed that Pulmonary Hypertension was present in 29% (n = 29) at 2 months of post-COVID and in 19% (n=19) at 6 months of post-COVID-19 disease. We found that there was a significant association of severity of COVID-19 disease with development of PH at 2 and 6 months post-COVID-19 disease. Among 29 patients who developed PH at 2 months, 27 were having severe COVID-19 disease while among 19 patients who had PH at 6 months, 18 were having severe COVID-19 disease.

Out of 29 subjects who were found to have PH at 2 months, 62.1% (n = 18) subjects had mild, 17.2% (n = 5) had moderate and 20.7% (n = 6) had severe PH at 2 months post-COVID-19 disease. At 6 months post-COVID-19 disease, out of 6 patients with severe PH, 1 patient remained with mild PH only while 3 patients had moderate PH, and 2 patients had severe PH. Similarly, all 5 moderate PH patients at 2 months of post-COVID-19 disease, left with mild PH at 6 months of post-COVID-19 disease. Out of 18 mild PH patients at 2 months of post-COVID-19 disease, PH resolved in 10 patients while remaining 8 patients had mild PH at 6 months. So, overall at 6 months of post-COVID-19 disease, 73.7% (n=14) had mild PH, 15.8% (n=3) had moderate and 10.5% (n=2) had severe PH.

In our study, we found that there was no significant association between the severity of COVID-19 and the severity of PH at 2 months and 6 months.

Table 3: Relationship of various parameters with PH at 2 and 6 months

Variable		Pulmonary Hypertension			
		at 2 months		at 6 months	
		Present	Absent	Present	Absent
Age (years)		53.55± 6.5	47.2± 8.1	53.95± 6.93	47.89± 8.04
Gender	Male	16	41	11	46
	Female	13	30	8	35
D-Dimer (mg/L)		3.16± 4.11	0.91± 0.77	4.15± 4.77	0.96± 0.81
CRP (mg/L)		71.72± 48.17	33.49± 41	73.47± 46.46	30.49± 23.94
Ferritin (ng/ml)		813.89±397.7	356.88±236.3	921.86±376.5	351.63±249.1
O_2 duration (days)		17.59	6.69	19.79	7.52
HTN		15	19	10	24
DM		18	21	14	25

Table 3 showed that patients with PH were older compared to patients without PH (53.55 vs 47.20 years, p<0.001 at 2 months and 53.95 vs 47.89 years, p=0.001 at 6 months). Starting from the premise that age could predict the evolution of PH, we did regression equation for age with PH.

PH = 2.682 – 0.020 * Age

The correlation coefficient (r) of 0.355 indicated a positive correlation between pulmonary hypertension and age, where age is the confounding factor. The positive correlation coefficient suggested that as age increases, there may be an increase in the likelihood of pulmonary hypertension. So, we tried to reduce this confounding factor by limiting age of study population to maximum of 60 years.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

Table 3 showed no significant relationship between gender of COVID-19 patients with PH was observed at 2 and 6 months. The patients who had PH at 2 and 6 months of post-COVID-19 disease had significantly raised d-dimer, CRP and ferritin levels (during COVID-19 illness). In COVID-19 patients, RV dilatation and dysfunction is common and its presence is associated with a prothrombotic, inflammatory state which is reflected by elevated D-dimer and CRP levels.[10] COVID-19 patients with PH had more frequently underlying comorbidities, including diabetes mellitus (p=0.003 at 2 months, p=<0.001 at 6 months) and hypertension (p=0.017 at 2 months, p=0.057 at 6 months). Studies have shown that hypertension and diabetes lead to a decrease in organ reserves, thus reducing the ability of hypertensive and diabetic patients to withstand viral attacks and leading to more severe COVID-19 disease.[11] No significant association was seen between coronary artery disease, chronic kidney disease, chronic liver disease, stroke, asthma, hypothyroidism and malignancy with PH. COVID-19 patients with PH at 2 months received higher duration of oxygen therapy during COVID-19 disease than without PH (17.59 vs 6.69 days) and similar findings were observed with PH at 6 months (19.79 vs 7.52 days).

Discussion

Coronavirus disease 2019 (COVID-19), a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by prominent pulmonary involvement.[12] The sustained hypoxic pulmonary vasoconstriction, uncontrolled pulmonary vascular remodelling and thrombosis in situ are the main mechanisms leading to pulmonary hypertension (PH) in patients with COVID-19.[3] Pulmonary Hypertension (PH) is a progressive disorder associated with increased morbidity and mortality.[13] Its prevalence varies largely depending on the characteristics of studied population (elderly, patients from intensive care units, or with associated co-morbidities like diabetes, hypertension), the severity of the COVID-19 disease (mild, moderate, or severe). That is why, we included patients of maximum age of 60 years in our study, as changes induced by aging on the lung and cardiovascular system are lesser, without pre-existent PH, or who suffered from a mild COVID-19 illness. After investigating 100 moderate to severe post-COVID-19 patients, using TTE, in our study group, an incidence 29% observed at 2 months and 19% at 6 months. This decrease in prevalence of PH over months could be due to the effect of anticoagulant treatment which was being given to our post-COVID-19 patients on follow up or due to recovery of lungs and pulmonary vasculature from acute COVID-19 disease.

An incidence of around 12% was given by Pagnesi et al.[12] and the study included only non-ICU COVID-19 patients and the 2D-ECHO was done during COVID-19 disease, i.e., within 3-13 days of the disease. Since, the study included only non-ICU patients, explains comparatively lower incidence of PH in their patients. The incidence of PH in post-COVID-19 patients in Tudoran C et al.[14] study was 13.3% at 4-8 weeks and 2.08% at 6 months post-COVID-19 disease. Their lower incidence could be explained as they included only mild-moderate COVID-19 patients while we included moderate and severe COVID-19 patients. PH gets aggravated by hypoxia and cytokine storm, which is seen more in severe COVID-19 disease,[14] so comparatively higher incidence was seen in our study. The incidence of PH in post-COVID-19 patients in Wolters AEP et al. study[15] was 29.7%, as they also conducted 2-D ECHO at 63 days (mean) after acute COVID-19 disease on 101 COVID-19 patients. The PH incidence in Norderfeldt J et al.[11] study was 39% which is higher comparatively as the study included only ICU COVID-19 patients.

The diagnosis of PH based on echocardiography was clearly correlated with increased duration of oxygen therapy in COVID-19 disease. This could be due to continued exposure to higher oxygen concentrations results in increased free radical production. These may damage the pulmonary epithelium and inactivates the surfactant, causes intra-alveolar edema,

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interstitial thickening, and fibrosis, leading to pulmonary atelectasis.[16] The production of reactive oxygen species directly stimulates endothelin-1 synthesis in the lung, which can lead to pulmonary hypertension.[17]

D-dimer levels are commonly elevated in COVID-19 patients which signifies a hyperfibrinolysis state and increased inflammatory burden induced in SARS-COV-2 infection.[18] The inflammatory cytokines causes the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system, and then increase the level of D-dimer. Increased CRP and ferritin levels are observed in inflammatory disorders and COVID-19 represents a systemic inflammatory condition with elevation of pro-inflammatory markers.[19] These inflammatory mediator leads to endothelitis and vasculitis which as a result increases the risk of pulmonary thrombosis.[20-21] The major mechanisms responsible for PH in COVID-19 patients were hypoxic pulmonary vasoconstriction, uncontrolled pulmonary vascular remodelling and thrombosis in situ.[3] Therefore, more severe the COVID-19 disease, more the hypoxic pulmonic vasoconstriction, more the systemic inflammation and more chances of developing PH. This could be the possible reason of raised serum ferritin and CRP and d-dimer levels in patients of COVID-19 with PH in our study.

One of the limitations of this study was that we relied only upon echocardiography for the determination of hemodynamic parameters and have not used any invasive methods–right heart catheterisation to verify our results, due to the pandemic restrictions and also we could not perform this procedure on a routine basis. Our study was also limited by small size of the study group.

Conclusion

PH was diagnosed on echocardiography in 29% of moderate to severe COVID-19 patients at 2 months post-COVID-19 disease. Furthermore, our data suggested that COVID-19-related PH might be reversible to some extent in the long term, as showed by decreased prevalence to 19% of PH at 6 months. Given the high morbidity and mortality associated with PH, we suggest vigilant attention to early diagnosis of PH and thereby, preventing its complications.

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ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

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