Original Article

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Prevalence of Post COVID-19 Pulmonary Arterial Hypertension and its Clinical Association with CT Severity Score among COVID-19 Pneumonia Survivors in a Tertiary Care Hospital of Western Odisha, India

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ABSTRACT

Introduction: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus targets the Angiotensin Converting Enzyme 2 (ACE2) receptor, which is abundantly present in two vital organs of the body, namely the lungs and the heart, making the pathogen devastating. Because these organs are closely linked in their pathophysiology, disease in one organ can affect the other. It has been observed that patients recovering from Coronavirus Disease 2019 (COVID-19) pneumonia can later develop fatal cardiac complications such as Pulmonary Arterial Hypertension (PAH) as a result of multiple and complex pathophysiological phenomena. PAH leads to right ventricular failure and death due to increased pulmonary vascular resistance. However, early diagnosis with appropriate medical management can increase survival and quality of life. The chest Computed Tomography (CT) severity score on High Resolution Computed Tomography (HRCT) of the lungs is a standard index for estimating the severity of pneumonia in hospitalised COVID-19 patients.

Aim: To estimate the prevalence of post COVID-19 PAH and to assess the association between chest CT severity score and post COVID-19 PAH among survivors of COVID-19 pneumonia.

Materials and Methods: A cross-sectional study was conducted in the Department of Cardiology, VIMSAR, Burla, Odisha, India, from October 2020 to October 2023, enrolling 854 patients with cardiac complaints in the post COVID-19 period. Severity of COVID-19 pneumonia was graded as mild, moderate, or severe according to the semiquantitative chest CT severity score method, based on the CT reports from the COVID-19 period. The enrolled patients were thoroughly examined; those with abnormal cardiac signs and Electrocardiography (ECG) or chest X-ray suggestive of underlying PAH underwent echocardiography. Diagnosis of PAH was performed according to the 2022 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Nonparametric statistical methods, such as the Chi-square test, were used to analyse qualitative data, whereas quantitative variables were expressed as means with standard deviations, and an unpaired t-test was used to compare means between two groups.

Results: The prevalence of PAH in the post COVID-19 period among pneumonia survivors was 12.1%. A total of 104 patients were diagnosed with PAH: 35 (33.7%) had severe pneumonia, 26 (25.0%) had mild pneumonia, and 43 (41.3%) had moderate pneumonia. The chest CT severity score was significantly associated with the development of post COVID-19 PAH.

Conclusion: Higher chest CT severity scores during acute COVID-19 pneumonia are associated with a greater risk of developing PAH in the post COVID-19 period. Proper screening of these patients can enable earlier detection of post COVID-19 PAH.

Keywords: Coronavirus Disease 2019, Computed Tomography, Hospitalisation, Pain

INTRODUCTION

The COVID-19 pandemic has become the deadliest in the 21st century, a brutal killer showing no mercy to any nation, irrespective of health infrastructure. The ACE2 receptor is the main entry point for SARS-CoV-2, abundantly present in two vital organs of the body, namely the lungs and the heart, which makes the pathogen devastating [1]. Because these organs are closely related both anatomically and physiologically, pathogenic processes in one organ can affect the other secondarily. It has been observed that patients who recover from COVID-19 pneumonia may later develop cardiac complications such as PAH as a result of multiple, complex pathophysiological phenomena [2]. The chest CT severity score on HRCT of the lungs is the standard index for estimating the severity of pneumonia in hospitalised COVID-19 patients [3]. PAH is a rare cardiac complication, but it is rapidly progressive and highly fatal, ultimately leading to right ventricular failure because of increased pulmonary vascular resistance, and death can occur without timely treatment [4-6]. Therefore, early diagnosis with proper medical management can increase survival and quality of life. A good number of studies have been published regarding post COVID-19 cardiac complications [7-12]. However, the literature examining the relationship between COVID-19 pneumonia and the development of PAH in the post COVID-19 period is limited [13-15]. Thus, an attempt was made to determine whether there is a relationship between the severity of pneumonia caused by SARS-CoV-2 infection and post COVID-19 hospitalisation with residual PAH, with the following objective. The present study aimed to estimate the prevalence of post COVID-19 PAH and to assess the clinical association between chest CT severity score and post COVID-19 PAH among COVID-19 pneumonia survivors.

MATERIALS AND METHODS

A hospital-based cross-sectional study was conducted in the Department of Cardiology, VIMSAR, Burla, Odisha, India, from October 2020 to October 2023. Ethical approval for the study was

obtained from the Institutional Ethics Committee, VIMSAR Burla (IEC No. 154/I.F.O-22).

Sample size calculation: The sample size was calculated based on the prevalence of PAH in the post COVID-19 period (P=7.69%), taken from a previous study by Tudoran C. et al., and the sample size (N) was calculated using the formula [13]:

$N = (Z\alpha)^{2*} P*Q/L^2$, {where $Z\alpha$=1.96 at 95% confidence interval, P (prevalence) =7.69;

Q=(100-P)=92.31; L=absolute precision=2}. So $N=\{(1.96)^2 \times 7.69 \times 92.31\}/4=682$;

As PAH is a rare cardiac manifestation, an extra 25% (172) participants were added to the number to obtain a larger sample size of 854.

Inclusion criteria: All patients above the age of 18 years with a history of COVID-19 pneumonia who attended the Cardiology Outpatient Department (OPD) for cardiac complaints such as shortness of breath, chest pain, pedal edema, etc., in the post COVID-19 period (i.e., more than 12 weeks after COVID-19 infection [16]). A total of 896 patients with some cardiac complaints in their post COVID-19 period were selected for the study.

Exclusion criteria: Patients with documented PAH (primary/secondary), any other heart disease, or Chronic Pulmonary Obstructive Disease (COPD) prior to COVID-19 infection; those without HRCT reports or films to ascertain the CT severity score; and those who did not give consent for the study were excluded. Thus, 42 patients were excluded and a total of 854 patients were finalised as the study participants after obtaining written informed consent.

In the current study, consecutive sampling (non-random sampling) was used to select the study participants. Participants were selected in a sequential manner, including all patients coming to the cardiology department for post COVID-19 cardiac check-ups who met the inclusion and exclusion criteria after obtaining written informed consent.

Study Procedure

A detailed history was taken to determine the present condition, severity of COVID-19 infection, and past history of any heart disease or COPD. A predesigned questionnaire was used to collect data from each participant regarding baseline characteristics, HRCT reports (to ascertain severity of pneumonia), pattern and location of pneumonia, clinical examination findings, chest X-ray, ECG, and echocardiography findings. HRCT lung findings from the COVID-19 infection available with the patient were thoroughly evaluated. Each of the five lung lobes (right upper, right middle, right lower, left upper, left lower) was visually scored on a scale of 0 to 5, where 0 indicates no involvement; 1, 2, 3, 4, and 5 correspond to <5%, 5-25%, 26-49%, 50%-75%, and >75% involvement of the lungs, respectively. The total chest CT severity score was derived as the sum of the individual lobar scores and recorded as the total score; 0 meaning no involvement and 25 meaning maximum involvement of the lungs [3,17]. Severity of pneumonia was graded as mild (7 or less), moderate (8-17), and severe (18 or more) as per the Chest CT severity score [18]. Patients were thoroughly examined for clinical findings such as pedal edema, cyanosis, parasternal heave, cardiomegaly with Right Ventricular (RV) apex, abnormal heart sounds (e.g., loud P2, narrow splitting), and lung sounds. All patients with abnormal cardiac signs, ECG, or chest X-ray suggestive of underlying PAH underwent echocardiography. As per the latest ESC guidelines, pulmonary hypertension is defined as a peak tricuspid regurgitation velocity >3.4 m/s, or >2.8 m/s to <3.4 m/s with at least two echocardiographic signs such as pulmonary acceleration time <105 ms and/or mid-systolic notching; right ventricle/left ventricle basal diameter ratio >1.0; or signs of increased right atrial pressure, e.g., inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration) [2]. RV dysfunction (RVD) is defined as Tricuspid Annular Plane Systolic Excursion (TAPSE) less than 17 mm, measured at the lateral tricuspid valve annulus in M-mode [19].

STATISTICAL ANALYSIS

Categorical data were represented in the form of proportions and percentages. Nonparametric statistical methods such as the Chi-square test were applied for analysis of qualitative data, whereas quantitative variables were expressed as the mean and standard deviation, and an unpaired t-test was used to compare means between two groups. A p-value <0.05 at the 95% confidence level was considered statistically significant, and p<0.001 was considered highly significant.

RESULTS

As depicted in [Table/Fig-1], the majority (58%) of the study subjects were male. A proportionately higher number of females (52.9%) were associated with post COVID-19 PAH compared with males, and this difference was statistically significant. Further analysis of the patients' ages showed that about 80% of those with post COVID-19 PAH belonged to the higher age group (≥40). Higher age during acute COVID-19 pneumonia was associated with subsequent development of PAH, which was statistically significant (p<0.05).

Parameters			Number (%) of patients (N=854)	Number (%) of patients with PAH; (N=104)		p-value (95% CI)
Sex	Male		495 (58%)	49 (47.1%)		0.008*
	Female		359 (42%)	55 (52.9%)		
Age (in years)	Younger age group 243 (28.4%)	18-29	112 (13.1%)	6 (5.8%)	21 (20.2%)	0.04*
		30-39	131 (15.3%)	15 (14.4%)		
	Higher age group 611 (71.6%)	40-49	211 (24.7%)	19 (18.3%)	83 (79.8%)	
		50-59	228 (26.7%)	36 (34.6%)		
		≥60	172 (20.1%)	28 (26.9%)		

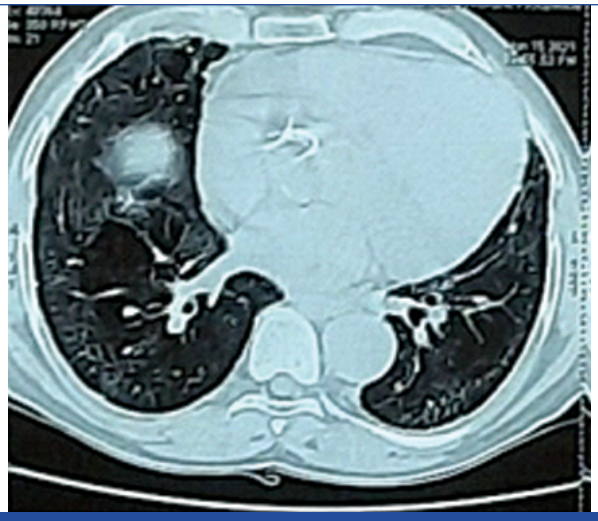
[Table/Fig-1]: Distribution of study participants according to sex and age (N=854). Chi-square (χ^2) test used; p-value considered statistically significant (p<0.05*)

When evaluating the HRCT thorax records from the acute COVID-19 period, mild, moderate, and severe pneumonia were observed in 412 (48.2%), 305 (35.7%), and 137 (16.0%) patients, respectively [Table/Fig-2]. Different patterns of parenchymal abnormalities, i.e., ground glass opacity [Table/Fig-3], parenchymal bands [Table/Fig-4], reticular opacity [Table/Fig-5], mosaic attenuation [Table/Fig-6], etc., were noted during CT thorax evaluation. The most frequent pattern of chest CT abnormality was ground glass opacity [Table/Fig-2,3] in 555 (64.9%) patients. The most common location for lesions in the lung was peripheral [Table/Fig-2,7] in 691 (80.9%) patients.

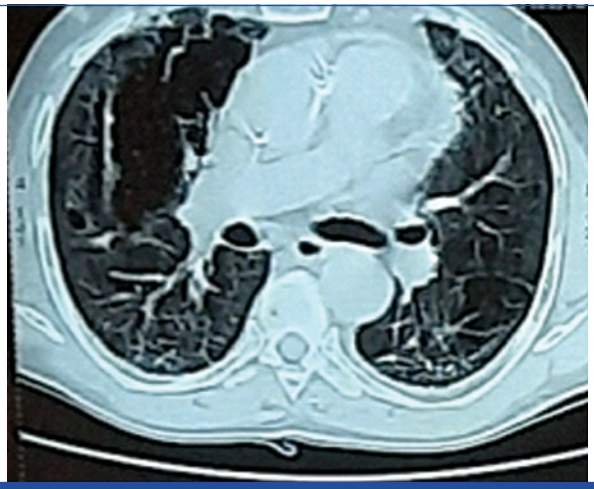
CT characteristics		Frequency (%)
Severity of Pneumonia	Mild	412 (48.2%)
	Moderate	305 (35.7%)
	Severe	137 (16.0%)
Patterns	Ground glass opacity	555 (64.9%)
	Parenchymal band	128 (14.9%)
	Reticular opacity	78 (9.1%)
	Mosaic pattern	93 (10.8%)
Location	Peripheral	691 (80.9%)
	Central	163 (19.1%)

[Table/Fig-2]: Characteristics of COVID-19 pneumonia based on CT findings during COVID-19 period (N=854).

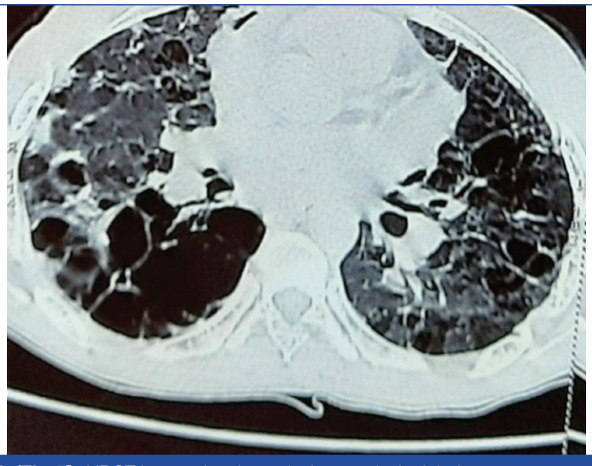
Clinical and laboratory features suggestive of congestive heart failure, such as raised JVP and cardiomegaly, were detected in 28 (3.2%) and 51 (5.9%) cases, respectively [Table/Fig-8]. Right



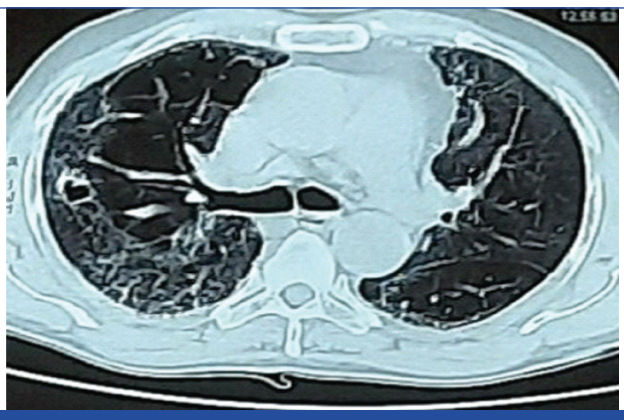
[Table/Fig-3]: HRCT image showing ground glass opacity in both right lungs.



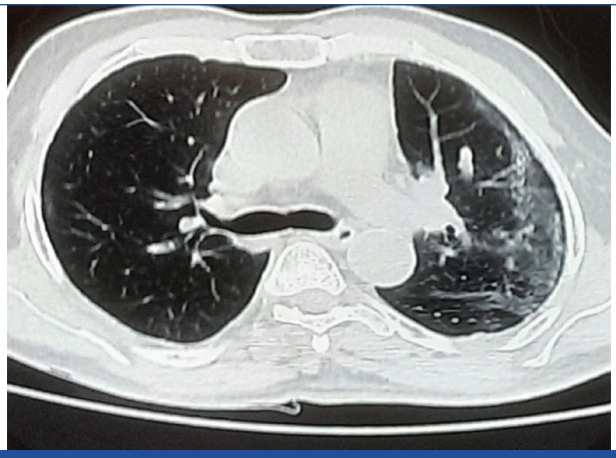
[Table/Fig-4]: HRCT image showing parenchymal band in both lungs.



[Table/Fig-5]: HRCT image showing reticular opacity in right lung.



[Table/Fig-6]: HRCT image showing mosaic pattern in both lungs.



[Table/Fig-7]: HRCT image showing pneumonic patch in peripheral left lung.

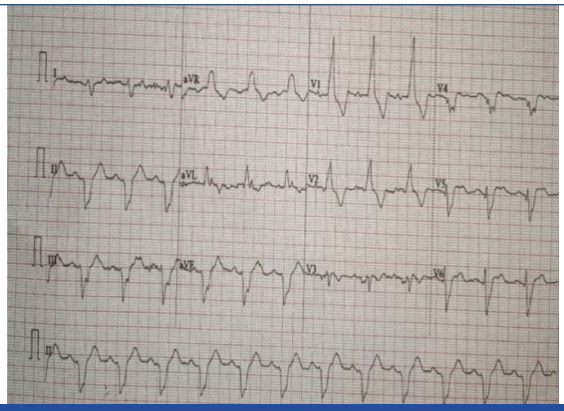
Ventricular Hypertrophy (RVH), Right Atrial Enlargement (RAE), and Right Ventricular Enlargement (RVE) were detected in 42 (4.9%), 56 (6.5%) and 46 (5.3%), of patients, respectively [Table/Fig-8-11]. A total of 108 (12.6%) patients had tricuspid regurgitation [Table/Fig-8,12]. A total of 104 (12.1%) patients were found to have PAH [Table/Fig-8,12], while the remaining 750 patients had no clinical findings suggestive of PAH. Right Ventricular Dysfunction (RVD) was detected in 28 (3.2%) patients [Table/Fig-8].

S. No.	Cardiac abnormalities		Number of patients (%)
1.	Clinical examination findings	Pedal oedema	24 (2.8%)
		Raised JVP	28 (3.2%)
		Cardiomegaly	51 (5.9%)
		Parasternal Lift	47 (5.5%)
		Loud P2	54 (6.3%)
		RV s3	26 (3.0%)
2.	Electrocardiography (ECG)	Right bundle branch block	26 (3.0%)
		Right Ventricular Hypertrophy (RVH)	42 (4.9%)
		Right Atrial Enlargement (RAE)	56 (6.5%)
		Right Axis Deviation (RAD)	39 (4.5%)
3.	Chest X-ray	Cardiomegaly	51 (5.9%)
		Right Atrial Enlargement (RAE)	56 (6.5%)
		Right Ventricular Enlargement (RVE)	46 (5.3%)
4.	Echocardiography	Dilated RV	52 (6.0%)
		Dilated RA	56 (6.5%)
		PAH	104 (12.1%)
		RV Dysfunction (RVD)	28 (3.2%)
		Tricuspid regurgitation	108 (12.6%)
		Pericardial effusion	13 (1.5%)

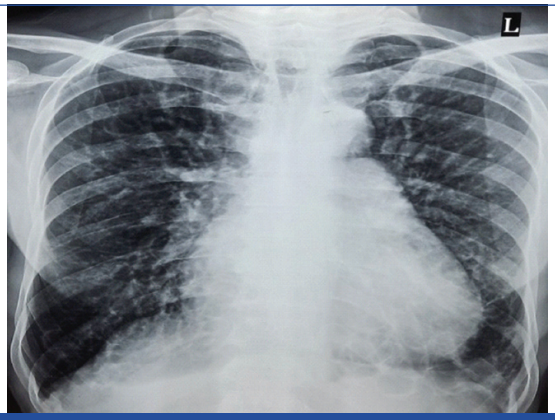
[Table/Fig-8]: Cardiac abnormalities among the study participants (N=854).

Clinical association of the severity of COVID-19 pneumonia, based on the chest CT severity score, with subsequent development of PAH in the post COVID-19 period is shown in [Table/Fig-13], which indicates that PAH was detected more commonly in 35 (33.7%) patients with severe pneumonia compared with 26 (25.0%) and 43 (41.3%) patients with mild and moderate pneumonia, respectively. A highly significant association was found between the severity of COVID-19 pneumonia and the subsequent development of PAH in the post COVID-19 period. In other words, as the severity of pneumonia increases, the likelihood of developing PAH in the post COVID-19 period increases.

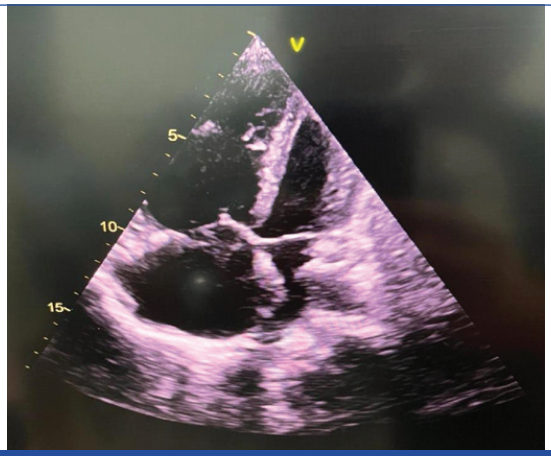
Similarly, a comparative analysis of mean CT severity scores during acute COVID-19 pneumonia, as recorded in [Table/Fig-14],



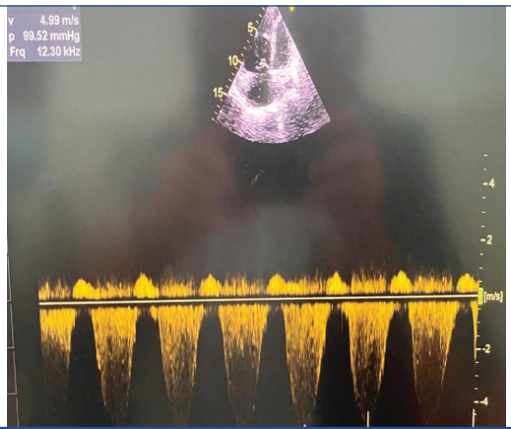
[Table/Fig-9]: ECG image of a patient showing Right Axis Deviation (RAD) and Right Ventricular Hypertrophy (RVH).



[Table/Fig-10]: X-ray chest image of a patient showing right ventricular and Right Atrial Enlargement (RAE) with RV apex.



[Table/Fig-11]: Echocardiographic image showing dilated RV, RA with shifting interatrial septum towards left in four chamber view suggestive of PAH.



[Table/Fig-12]: Doppler echocardiographic image showing peak tricuspid gradient suggestive of severe PAH and tricuspid regurgitation.

showed that the mean CT score among patients (Group 1) who subsequently developed post COVID-19 PAH was 21.32±3.17,

Severity of COVID-19 pneumonia based on CT score	PAH in post COVID-19 period		p-value (95% CI)
	Patients having PAH (Group 1)	Patients not having PAH (Group 2)	
Mild	26 (25%)	386 (51.5%)	<0.001**
Moderate	43 (41.3%)	262 (34.9%)	
Severe	35 (33.7%)	102 (13.6%)	
Total	**104 (100%)**	**750 (100%)**	

[Table/Fig-13]: Showing association of Chest CT severity score with Post COVID-19 PAH among the study subjects; (N=854).
Chi-square (X^2) test used; p-value considered statistically highly significant (p<0.001**)

Patient status	No. of patients	Mean CT score (Mean±SD)	t- Statistic	p-value; (95%CI)
Patients having PAH (Group 1)	N1=104	21.32±3.17	**28.681**	**<0.001****
Patients not having PAH (Group 2)	N2=750	10.53±3.65		

[Table/Fig-14]: Comparison of mean chest CT-scores between two groups of patients having PAH and without PAH.
Un-paired t-test used; p-value considered statistically highly significant (p<0.001**)

whereas that among patients who did not develop PAH (Group 2) was 10.53±3.65; the difference in means was highly statistically significant. This suggests that patients with higher CT severity scores are more prone to developing post COVID-19 PAH.

DISCUSSION

In the present study, the prevalence of PAH in the post COVID-19 period among patients with prior COVID-19 pneumonia was estimated at 104 (12.1%), higher than that reported by Tudoran et al., who found a prevalence of 7.69% [13]. The difference in prevalence between the studies might be due to differences in inclusion criteria. Tudoran et al., included patients with mild to moderate pneumonia, whereas the current study included patients with pneumonia of all severities (i.e., mild, moderate, and severe) [13]. Secondly, Tudoran et al., included patients diagnosed with COVID-19 by Reverse Transcription Polymerase Chain Reaction (RT PCR) two months prior [13], whereas the present study included patients with a longer recovery period (i.e., 12 weeks) after COVID-19 infection, in accordance with National Institute for Health and Care Excellence (NICE) guidelines [16]. In a study by Taha HA et al., the prevalence of PAH was unusually high, i.e., 70%, compared with the present study, although PAH is a rare cardiac complication [20]. The higher prevalence in their study might be due to a small sample size and inclusion of critically ill patients with severe pneumonia during the subacute period. In a study by Wolters AEP et al., a higher proportion (i.e., 29.7%) of patients were detected to have PAH compared with the present study; this may be due to the inclusion of hospitalised patients during the COVID-19 period and a smaller sample size, which may account for the higher PAH proportion [21].

Furthermore, in the present study, there was a proportional increase in the number of post COVID-19 PAH cases with increasing severity of pneumonia during COVID-19 infection, as evidenced by the chest CT score. The majority of PAH cases were associated with a history of moderate to severe COVID-19 pneumonia, suggesting that the likelihood of developing post COVID-19 PAH is higher in patients with moderate to severe pneumonia; the mean CT severity score among patients with PAH was significantly higher than among those without PAH. In a similar study, Tudoran et al., also observed a clinical correlation between PAH and HRCT severity score [13]. However, they used Pulmonary Artery Systolic Pressure (PASP) to assess PAH severity and correlated it with the severity of pneumonia. By contrast, according to the newer ESC and American Heart Association (AHA) guidelines [6], the severity of PAH cannot be graded using quantitative echocardiographic parameters such as PASP alone; rather, the probability of PAH (low, intermediate, or high) can be assessed based on echocardiographic findings.

Besides the study by Tudoran C et al., a few other studies, such as Yildiz M et al., and Raoufi M et al., found an association between the severity of pneumonia and post-COVID-19 PAH indirectly by comparing the severity of COVID-19 pneumonia with pulmonary artery diameter, which strongly supports the current study [13-15]. Furthermore, a study by Francone M et al., found a positive correlation between CT severity score and markers of inflammation and coagulation, such as CRP and D-dimer [22]. Persistence of such inflammatory and hypercoagulable states in post-COVID-19 patients [23,24] may be responsible for chronic pathophysiological changes in the pulmonary vasculature, leading to chronic PAH in post-COVID-19 patients [25].

Limitation(s)

The current study was conducted at a single centre; however, a multicenter study could have provided findings applicable to a relatively wider population. The current study is cross-sectional, whereas long-term follow-up of the patients could have provided more valuable information. Our findings were based on the HRCT score during COVID-19 infection, whereas many patients were diagnosed by chest X-ray or throat/nasal swab testing and did not undergo HRCT during the pandemic due to limited resources and restrictions. Lastly, noninvasive echocardiographic findings for assessment of PAH could not be validated with invasive methods such as right heart catheterisation due to pandemic restrictions.

CONCLUSION(S)

PAH is a fatal cardiac complication during the post-COVID-19 period, with a prevalence of 12.1% among survivors of severe COVID-19 pneumonia; this cannot be overlooked. Higher chest CT severity scores during COVID-19 infection are associated with a higher likelihood of developing severe cardiac complications such as residual PAH in the post-COVID-19 period. Hence, chest CT severity score can be used as a valuable predictive tool to anticipate and detect PAH in the post-COVID-19 period.

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