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ADULT CARDIOLOGY

Echocardiographic Assessment of Right Ventricular Function in COVID-19 Recovered Patients at a Tertiary Care Hospital

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ABSTRACT

Objective: To detect residual RV dysfunction on a right ventricle focused Transthoracic Echocardiography (TTE) in COVID-19 infection survivors with lung involvement.

Study Design: Analytical cross-sectional study design.

Place and Duration of Study: Combined Military Hospital Abbottabad Pakistan, from Feb 2022 to Apr 2022.

Methodology: A total of 87 patients who had suffered from and survived COVID-19 infection with definite involvement on CT scans of the chest were studied after discharge. Echocardiography was done to determine the RV anatomical and functional para-meters to determine the relationship between extent of lung involvement and transthoracic echocardiographic parameters. Data was entered in Microsoft excel and exported to SPSS version 23 for analysis.

Results: The initial sample size was of 87 patients. Due to suboptimal ECHO studies 7 cases were excluded. Males represented 62.5% (n=50) and females 37.5% (n=30). The ages ranged from 27 to 80 years, mean 53.08±12.77 years. Based on the CT severity score severe infections were 61.3 %(n=49) and mild 38.8% (n=31). The CTSS ranged from 6 to 30 with a mean of (17.74±7.13). In our study we found that on TTE, there was a statistically significant difference in 2 of the anatomical parameters; RVOT PLAX (RVOT diameter in Parasternal long axis view) [27.4 vs 28.3; p=0.02], RVOT-Dis (Distal RVOT dia) [22.8 vs 24; p=0.01]. In addition, there was a statistically significant difference in all the functional parameters of RV function TDI S vel (Systolic Tissue Doppler Velocity of the Tricuspid Annulus by Tissue doppler imaging) [7 vs4.9; p<0.0001], RIMP-PW (Right Ventricular Index of Myocardial Performance by Pulse wave doppler) [0.46 vs0.38; p<0.0001], RIMP-TDI (Right Ventricular Index of Myocardial Performance by Tissue doppler imaging) [0.57 vs 0.48; p<0.0001]. RV-FAC (RV-Fractional Area Change) was statistically insignificant. [42.8% vs 43.2%; p=0.6].

Conclusion: Our study showed that in patients with definite lung involvement on chest CT scans, functional echocardio-graphic parameters of Right ventricular function were affected in line with the severity of lung involvement.

Keywords: COVID-19, Right ventricular function, RIMP, RVOT.

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INTRODUCTION

The origins and devastating effects of the COVID-19 pandemic (caused by the SARS-CoV-2 virus) are common knowledge. COVID-19 mortality is mainly due to ARDS and life-threatening cardiovascular complications.[1] Cardiovascular involvements in COVID-19 can be due to direct damage from the virus (such as myocarditis, heart failure, and arrhythmia) and indirect damage (such as thromboembolism and metabolic disorder) due to the release of cytokines (interleukin 6), coagulopathy, and insulin resistance.[2,3]

Given the direct anatomical connection of the lungs with the right ventricle (RV); intuitively, it is likely to be affected leading to RV pressure overload. RV dysfunction is frequently associated with moderate to severe ARDS and is one of the major determinants of mortality.[4,5] The pulmonary parenchymal involvement with or without ARDS in COVID-19 leads to hypoxia which induces pulmonary vasoconstriction leading to increased pulmonary vascular resistance (PVR).[1] The increased PVR places an increased load on the RV. Physiologically speaking, the thin walled is more susceptible to sudden increases in afterload as happens in COVID-19 and ARDS. Autopsy reports on COVID-19 patients have shown RV dilatation.[6]

The aim of our study was to detect residual RV dysfunction on a right ventricle focused Transthoracic Echocardiography (TTE) in COVID-19 infection survivors with lung involvement.

METHODOLOGY

This analytical cross sectional study was conducted in Combined Military Hospital Abbottabad, from February to April 2022 on patients who had recovered from COVID-19 infection after approval from ERC (Ltr# 2020-012-17044). Study population was recruited using non-probability, consecutive sampling.

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Sample Size:. We recruited all COVID-19 patients (n=87) who came for echocardiographic assessment.

Inclusion Criteria: In this study we included patients aged 20-80 years, who had contracted COVID-19 infection documented by PCR test, along with radiological abnormalities characteristic of COVID-19 infection on a high-resolution CT scan (HRCT) during the hospital admission for COVID-19.

Exclusion Criteria: Patients with a suboptimal ECHO studies (A suboptimal ECHO studies was defined in which the entire list of pre-determined indices of TTE could not be acquired) were also excluded from the study.

The patients recovered from COVID-19 infection as documented by PCR were discharged. Finally, a post discharge TTE study after consent should have been available.

All TTE studies were done with ECG gating, and the measurements performed according to Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[7] The TTE was performed on a Vivid E9 (Vivid I; GE Vingmed Ultrasound AS, Horten, Norway) echocardiography machine using the M5S Echocardiographic probe (4.6 MHz). Where the images were suboptimal, an attempt was made to use the 4V Echocardiographic probe (4.0 MHz) which can simultaneously image in 2 planes and generate 3D images. All echocardiograms were performed by a Cardiologist Board certified in Echocardiography. The imaging plane chosen for the imaging of the RV was the RV-focused apical 4 chamber view. Tissue harmonic imaging was employed to improve image quality. The image settings were chosen to provide a clear delineation between the endocardial and myocardial borders. When measuring the RV systolic and diastolic areas, the myocardial trabeculations were included as a part of the RV cavity. All studies were done in greyscale, where the greyscale images did not allow for adequate delineation of endo-myocardial interface, we change the greyscale setting to other colors.

Settings for the doppler measurements were as follows;

The sweep speed was set to 100cm/sec; the baseline and scale was shifted to optimize the entire doppler signal of interest as large as possible. All doppler studies were done in greyscale. For PW Doppler, the gain was set to ensure a clear doppler envelope without excess background noise. Sample volume was set at 4-5mm. For measurements, the PW Doppler sample volume was placed in the center of the RVOT, about 5–10mm proximal to the PV. Sweep speed was set at 100cms^{-1}.

Image analysis was done with the analysis tools on the machine at the time of examination. HRCT chest was performed on a GE 128 slice scanner and lung involvement was based on a 40-point CT score.[8] A score ≥20 was used to represent severe COVID-19; a score of ≤19 represented mild COVID-19 infection. CT scores were added from the relevant reports.

The data was summarized using descriptive and inferential statistics. Mean and SD were reported for the scale variables; and frequencies reported for the nominal variables. A comparison of means was done for the echocardiographic variables between the "mild" and "severe" group using the t-test. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

The initial sample size was of 87 patients. Due to suboptimal studies 7 cases were excluded. Males represented 62.5% (n=50) and females 37.5% (n=30). The ages ranged from 27-80 years, mean 53.08±12.77 years. Based on the CT severity score severe infections were 61.3%(n=49) and mild 38.8%(n=31). The CTSS ranged from 6-30 with a mean of (17.74±7.13). Showing hemodynamic parameters from echo are given in Table-I.

Table-I: Echocardiographic parameters of the study population.

	COVID Severity	n	Mean	SD	*p*-value
Anatomical Parameters					
RVOT PLAX (mm)	Mild	49	27.41	1.836	0.02
	Severe	31	28.35	1.854	
RVOT-Prox Dia (mm)	Mild	49	28.22	4.575	0.63
	Severe	31	27.71	4.839	
RVOT-Dis Dia (mm)	Mild	49	22.84	2.230	0.01
	Severe	31	24.06	2.128	
RV Dimesions					
RV Basal (mm)	Mild	49	37.53	1.721	0.6
	Severe	31	37.35	1.723	
RV mid (mm)	Mild	49	29.51	3.150	0.07
	Severe	31	30.77	2.963	
RV long (mm)	Mild	49	75.14	3.736	0.9
	Severe	31	75.13	3.452	
RV Functional Parameters					
TAPSE (mm)	Mild	49	20.45	2.319	<0.0001
	Severe	31	12.68	2.056	
RV- FAC (%)	Mild	49	42.857	4.8088	0.6
	Severe	31	43.323	4.3695	
TDI S vel (cm/sec)	Mild	49	7.100	.6416	<0.0001
	Severe	31	4.948	.7247	
RIMP-PW	Mild	49	.4665	.02496	<0.0001
	Severe	31	.3871	.02610	
RIMP-TDI	Mild	49	.5710	.02134	<0.0001
	Severe	31	.4835	.02893	

Table Legend: RVOT= Right ventricular out flow tract; RVOT PLAX (RVOT diameter in Parasternal long axis view), RVOT-Prox (Proximal RVOT diameter), RVOT-Dis (Distal RVOT dia), RV= Right Ventricle; RV Basal (RV Basal diameter in dedicated RV apical view), RV mid(RV mid diameter in dedicated RV apical view), RV long(RV Long axis length in dedicated RV apical view), TAPSE (Tricuspid Annular plane systolic excursion), RV-FAC (RV-Fractional Area Change), TDI S vel (Systolic Tissue Doppler Velocity of the Tricuspid Annulus by Tissue doppler imaging), RIMP-PW (Right Ventricular Index of Myocardial Performance by Pulse wave doppler), RIMP-TDI (Right Ventricular Index of Myocardial Performance by Tissue doppler imaging)

In our study we found that on TTE, there was a statistically significant difference in 2 of the anatomical parameters; RVOT PLAX and RVOT-Dis between the mild and severe disease groups. In addition, there was a statistically significant difference in all the functional parameters of RV function (TAPSE, TDI S vel, RIMP-PW, RIMP-TDI) except FAC. FAC was statistically insignificant because it is indi-rectly calculated from the RV dimensions in the apical views (RV Basal, RV mid, RV long) which were nor-mal. Comparison of the echocardiographic variables between the 2 groups.

DISCUSSION

COVID-19 can affect the RV by a multitude of mechanisms. The incidence of pulmonary embolism is higher in COVID-19 patients. This additional factor could be responsible for RV dysfunction. The exact extent of RV dysfunction depends on the degree of pulmonary embolism. Acute pulmonary embolism leads acutely to hypoxic pulmonary vasoconstriction and increased PVR. This increased PVR places an afterload strain on the RV, potentially leading to its failure,[9] COVID-19 is a disease known to cause dysregulation of the coagulation pathways potentiating deep vein thrombosis,[10] an incidence higher compared to the general population on autopsy studies. Diffuse microthrombi formation in the pulmonary circulation has been noted, possibly secondary to the inflammatory response in ARDS.[11,12]

Besides the indirect effect on the right ventricle through the lungs, direct myocardial involvement by COVID-19 is also a possible mechanism for RV damage. The pathological findings in a limited number of autopsy studies vary. One study showed lymphocytic myocarditis in the absence of pulmonary symptoms,[13] while another showed scattered myocyte necrosis without any significant lymphocytic infiltration in these patients.[14] A case report has shown mononuclear cell infiltrates in the RV of a COVID-19 patients.[10] Angiotensin converting enzyme-2 (ACE-2) has been implicated in the cardiotoxic effects of SARS-CoV-2.[15,16] the extensive expression of ACE-2 in the cardiomyocytes, endothelial cells, cardiac pericytes and fibroblasts makes them potential targets for the ACE-2 mediated SARS-CoV-2 effects. The endothelial and pericyte dysfunction and the proinflammatory effects of Angiotensin 2 along with the aforementioned coagulopathy may provide a possible explanation of micro and macro vascular dysfunction,[6,17] that can contribute to RV dysfunction.

Through all the above mechanisms, the course of acute COVID-19 may be complicated by RV involvement. In the long term, development of pulmonary fibrosis in SARS-CoV and ARDS patients (post-recovery) has been reported.[18]

As mentioned above, the combined effects of SARS-CoV-2 on the heart and lungs may eventually lead to long term morphological and physiological consequences for the RV. It was with this idea that we conducted this study.

Our study findings as delineated in Table-II show that on TTE there was a statistically significant difference in 2 of the anatomical parameters; RVOT PLAX and RVOT-Dis between the mild and severe disease groups. In addition, there was a statistically significant difference in all the functional parameters of RV function (TAPSE, TDI S vel, RIMP-PW, RIMP-TDI) except FAC. FAC was statistically insignificant because it is indirectly calculated from the RV dimensions in the apical views (RV Basal, RV mid, RV long) which were normal. It is obvious that while there were no significant differences in anatomical dimensions in the patients with mild and severe disease there were significant RV functional changes between the 2 groups. In a cohort of 105 patients vs age and sex matched controls, Akkaya *et al*. found that RV function parameters including TAPSE, RVFAC, TDI S vel, RIMP-TDI were significantly reduced at 3 months after mild COVID-19 infection.[19] The same authors also looked at Global longitudinal strain values and RV free wall strain values in the 2 groups and found them both to be reduced. Asgarpur *et al*. studied the early and late (at 2 weeks) echocardiographic parameters of RV size and function as well as both related to O(2)/F(i)O(2) ratio (this ratio denotes ARDS severity) in COVID-19 patients with ARDS. They found that the early parameters were normal however, RV dysfunction and dilatation was present at 2 weeks which correlated with the severity of ARDS.[20] Although a generalization, these 2 studies show that there is late RV dysfunction related to COVID-19, a finding echoed by our study. In other studies however, while the prevalence of RV strain was high in intubated COVID-19 patients, the RV strain did not indicate the severity of COVID-19

infection.[21] Lower RV longitudinal strain has been found to be of prognostic significance in patients with COVID-19 infection.[22] The similar RV sizes in the severe group in our study may represent the normalization of RV sizes over a period of time. Rossi et al concluded after a study in a study of 25 patients that there was a phase after COVID-19 infection in which patients were symptomatic and showed pulmonary hypertension and RV dysfunction on echo. However, over a period of time these changes resolved.[23] It is unclear if we can extrapolate these findings to our study.

The findings in our study are important because of the prognostic implications. This has been established by quite a few studies. Negatively altered RV functional parameters are important predictors of mortality. In a systematic review and meta-analysis that looked at prognostic utility of RV dysfunction in COVID-19 survivors, it was found that every 1% fall in FAC and 1mm fall in TAPSE was independently associated with mortality.[24] Another systematic review and meta-analysis has shown similar prognostic implications of RV dysfunction and RV dilation.[25]

To our knowledge this is one of the first studies done on RV function in COVID-19 patient population in Pakistan with a correlation to the extent of lung involvement. All echocardiographic parameters of RV function outlined by the Chamber quantification guidelines of the American Society of Echocardiography,[7] except 3D echocardiography were studied.

LIMITATIONS OF THE STUDY

The main limitations of any imaging study are those of the investigative tool being used. Although echocardiography is the first line investigation to evaluate cardiac function, it can be hampered by difficult acoustic windows due to patient body habitus. In our study we had to omit 7 cases from our analysis because of this limitation. Measuring myocardial velocities using the doppler technique can give erroneous results in case of difficult alignment, however this is mostly operator dependent.

It is hard to say whether these findings represent possible RV pressure overload secondary to lung involvement or RV involvement by the COVID virus itself. This would need further evaluation with cardiac magnetic resonance imaging (CMR) because of its strength in tissue characterization. Every imaging study of the RV is limited by its complex three-dimensional geometrical structure. Although, our study did not find statistically significant differences RV dimensions, however the gold standard investigation in this case is CMR. It would be worthwhile looking at in a similar study population with CMR as the investigative tool. Because of the imaging strengths of CMR it doesn't require large study population as even small changes in cardiovascular changes are detectable. However, CMR cannot provide doppler data. Furthermore, it would have been ideal to index RV dimensions according to body surface area (BSA), but normal RV dimensions indexed to BSA don't exist. Because of its superior tissue characterization abilities, RV involvement in COVID-19 demonstrated on cardiac MRI will be the subject of future research.

CONCLUSION

Our study showed that in patients with definite lung involvement on chest CT scans, functional echocardiographic parameters of Right ventricular function were affected in line with the severity of lung involvement.

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Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

NB: Concept, study design, analysis, manuscript writing

SH: Intellectual contribution, concept and final approval

RY: Analysis, manuscript writing and proof reading

MJD: Design, analysis and manuscript writing

HK: Data collection, data analysis and review of article

JA: Analysis, manuscript writing and proof reading

AS: Analysis, manuscript writing and proof reading

RJ: Analysis, manuscript writing and proof reading

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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