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Echocardiographic Findings, Correlation with Cardiac Biomarkers along with their Prognostic significance in Patients with COVID-19 Infection- An Experience from Pakistan

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Abstract

Background: Trans-thoracic Echocardiography (TTE) in COVID-19 patients can result in significant healthcare personnel's exposure and requires personal protective equipment (PPE) in a resource-limited and lower middle-income countries. There is scarce data on echocardiographic findings in COVID-19 patients from countries like Pakistan. This study was done to evaluate the spectrum of echocardiographic findings with indications in COVID-19 patients and their correlation with cardiac and infective biomarkers.

Materials and methods: A retrospective observational study was conducted in a large tertiary care hospital of Pakistan. Patients with a SARS-Cov2 RT-PCR positive result, who have undergone TTE were included. Echocardiography was performed by Echo-technologists using portable machines with all the PPE. Findings were reported in electronic medical records and were reviewed from March 2020 to July 2020 which was the first outbreak

period in Pakistan. Patients with poor echocardiographic windows or incomplete records were excluded.

Results: A total of 125 patients were included in the study. Majority 63.2%(79) were males, 19.4%(24), 33.6%(42), and 47.2%(59) had mild, moderate and severe COVID-19 disease respectively. Patients with critical COVID-19 requiring invasive mechanical ventilation were 21.6%(27). Mean peak Troponin levels were 4.48±20.07 ng/ml, median peak C-Reactive Protein levels were 135mg/l (IQR 63.65-191), median Pro-BNP levels 842(IQR 205-2971) and peak D-Dimer levels were 3.75 ng/ml (IQR 1.00-9.125). Common indications for TTE were LV function assessment in 55.2%(69), elevated cardiac biomarker (troponin-I) in 38.4% (48), suspected pulmonary embolism and RV assessment in 4.8%(6) and stroke

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work up in 1.6%(2) patients. Evidence of new myocardial infarction was reported in 12%(15) and evidence of myocarditis in 24.8%(31). Left ventricular segmental wall motion abnormalities were observed in 10.4%(13) and generalized global changes in 6.4%(8). Change in the management was noted in 16% (20) patients after TTE. Only 4%(5) had prior echocardiogram available for comparison and among those new findings were present in 2.4%(3). Using spearman correlation, weak inverse relation was found between ejection fraction and troponin(r-0.367, p-value<0.001), peak CRP(r-0.238, p=0.009), peak D-Dimer(r-0.27, p=0.003) and pro-BNP levels(r- 0.281, p=0.003). Approximately 17.6%(22) died, with a higher mortality among patients with echocardiographic abnormalities compared to those with normal echocardiogram (13 of 43[30.2%] vs 19 of 82[23.1%]; P-value=0.007). Similarly patients with impaired LV systolic function showed a higher mortality compared to those with normal LV function (15.4 % vs 28.6%), but the result was not statistically significant (p=0.205).

Conclusion: LV function assessment was the most common indication for TTE and was normal in most COVID-19 patients. There was a weak co-relation between LV function and cardiac biomarkers. Echocardiographic evaluation resulted in a change in the management in less than one-third of patients. Overall mortality was higher in the patients with echocardiographic changes. Further larger studies are required to confirm the results of this study.

Introduction

On 10th March 2020 World Health Organization declared Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, a pandemic. More than 10 million cases and 500,000 deaths were recorded worldwide by the end of June 2020 [1]. Myocardial injury has been observed in 20-30% of all the patients and the infection can itself worsen pre-existing cardiovascular disease [2-5]. Many mechanisms have been identified that contribute to various cardiovascular complications in Covid-19 patients including direct myocardial injury due to entry and binding of the SARS-CoV-2 virus on angiotensin-converting enzyme-2 (ACE-2) receptors, with high expression in the heart and lungs along with the indirect effects through systemic inflammation and cytokine storm, adverse effects of various therapies and prothrombotic state [6]. Zhou et al reported heart failure occurring in 52% of patients who died [7]. Although literature and studies on myocardial injury are increasing, studies on echocardiographic findings and their correlation with cardiac biomarkers are few. As noninvasive, echocardiography requires personal exposure and personal protective equipment (PPE)'s use for COVID-19 patients, which prompted appropriate recommendations from various societies, including the American Society of Echocardiography (ASE) and EACVI [8,9]. Guidelines recommend not performing routine echocardiography in COVID-19 patients, carrying out focused cardiac ultrasound studies in situations proven to benefit the patients, and shortening scan times to reduce the exposure to medical professionals and echo technologists. Echocardiography can assist in differentiating cardiac events, and identifying short-term prognosis by identification of Covid-19 associated cardiovascular complications [10]. TTE resulted in changes in the management of around 33% of patients in a multi-center global

evaluation of echocardiography in patients with COVID-19 [11] but this proportion was lower by 16.7% in a study by Jain et al [12]. Certain echocardiographic features such as right ventricular longitudinal strain, impaired left ventricular (LV), and right ventricular (RV) function were found to be predictors of mortality in studies by Yuman et al [13] and Rath et al [14]. Hani et al found elevated levels of D-Dimers and C-Reactive Proteins in patients with reduced RV function [15]. This study was done to determine the spectrum of echocardiographic findings in Covid-19 patients, their correlation with cardiac biomarkers and to determine the prognostic significance of echocardiographic abnormalities, and whether there was any change in the management of patients after TTE. This article was also previously presented as an abstract at PULSE 2022, Conquering heart failure on January 16, 2022.

Methodology

A retrospective cross-sectional study was conducted from March to July 2020 (The first COVID19 outbreak period in Pakistan), at the Aga Khan University Hospital, Karachi-Pakistan after ethical approval from the Ethical Review Committee. Patients with at least one SARS-Cov-2 RT-PCR positive result, who have undergone TTE were included using non-probability consecutive sampling. Patients with poor echocardiographic windows or incomplete medical records were excluded. A retrospective review of the records of patients with SARS-Cov2 RTPCR positive results was performed using a pre-designed data entry form to collect demographic characteristics, comorbidities, clinical characteristics, and echocardiographic findings.

Echocardiography was performed by echo-technologists using portable ultrasound machines (GE Healthcare) after approval from the senior cardiologist regarding TTE's requirement and later on, the findings were reviewed by the reporting cardiologist. Indications were classified into cardiovascular events (rising cardiac biomarkers, acute coronary syndrome, myocarditis, pulmonary embolism) or shock/hemodynamic instability. Study quality was evaluated by the reporting cardiologist in categories such as mildly limited, moderately limited, severely limited, and non-diagnostic [12]. Significant myocardial injury was defined as a peak cardiac troponin I level >1 ng/mL (reference <0.04 ng/mL). Trop-I and PBNP limits were defined as elevated high sensitivity Trop-I and NT- pro-BNP by values greater than the 99th percentile. Whereas the severity of Covid-19 was based on Chinese CDC guidelines and NIH Pakistan Guidelines [16,17]. It defined mild COVID-19 disease as having fever, cough, or change in the sense of smell or taste with no dyspnea. Moderate COVID-19 disease was defined as dyspnea with radiographic evidence of lower respiratory tract disease and blood oxygen saturation above 94%, while severe COVID-19 disease included dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 94%, PaO2/FiO2 ratio or P/F < 300, and/or lung infiltrates > 50% within 24 to 48 hours. Similarly, critical COVID-19 disease was defined as the development of respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF). The value for the diagnosis of pulmonary hypertension is considered to have pulmonary artery systolic pressure (PASP) of more than 40 mm of Hg estimated on TTE. Outcomes assessed were death, mechanical ventilation, and the length of hospital stay.

Data Analysis

Data entry and analysis were done on SPSS version 23. Patients were given codes to maintain confidentiality. Continuous variables were described as mean ± standard deviation, or Median (Interquartile ranges) after normality tests. Categorical

variables were expressed as percentages. Normally and abnormally distributed quantitative variables were compared using the student's test and the Mann-Whitney U test, respectively. A Chi-square test was done for the comparison of categorical data. Correlation with myocardial biomarkers, echocardiographic parameters, and mortality was also assessed. P-value< 0.05 was taken as significant.

Results

A total of 125 patients were included in the study. The majority 63.2% (79) were males. Out of the total COVID-19 patients 19.4% (24), 33.6%(42), and 47.2%(59) had mild, moderate and severe COVID-19 disease respectively. However, critical COVID-19 and those on invasive mechanical ventilation were 21.6% (27). Common indications for TTE were assessment of LV function due to hemodynamic instability/shock in 55.2%, troponin elevation or other elevated cardiac biomarkers in 38.4% (48), suspected pulmonary embolism and RV assessment in 4.8% (6), and stroke workup in 1.6% (2) patients. Evidence of new myocardial infarction was reported in 12% (15) and evidence of myocarditis in 24.8% (31). **Figure 1** has shown common echocardiographic abnormalities found on TTE in which pulmonary hypertension (PH) was found in 17.6% (22), left ventricular segmental wall motion abnormalities were observed in 10.4%(13), and generalized global changes in 6.4%(8).

On the other hand, **Table 1** has shown the comparison of different clinical parameters among patients with and without echocardiographic abnormalities.

Patients who had changes in the management after TTE were 16%(20). Only 4%(5) patients had prior echocardiograms available for its comparison and among these, new findings were present in only 2.4%(3) patients.

Mean peak Troponin levels were 4.48± 20.07 ng/ml, median peak C-Reactive Protein levels were 135mg/l (IQR 63.65-191), median Pro-BNP levels were 842(IQR 205-2971) and peak D-Dimer levels were 3.75 ng/ml (IQR 1.00-9.125). We have also observed that the peak D-Dimer and peak

Troponin levels were higher in patients with echocardiographic abnormalities, as shown in **Table 2.**

Using spearman's correlation, weak inverse relation was found between ejection fraction and troponin (r-0.367, p-value<0.001), peak CRP (r-0.238, p=0.009), peak D-Dimer (r-0.27,p=0.003) and pro-BNP levels (r-0.281, p=0.003), as shown in **Table 3.**

Approximately 17.6% (22) patients died and there was no statistically significant difference in the mortality rate among patients with normal and impaired LV systolic function (15.4 % vs 28.6%) but there was a higher mortality among patients with overall echocardiographic abnormalities compared to those with normal echocardiogram (13 of 43 [30.2%] vs 19 of 82 [23.1%]; P value=0.007) as well in patients with PH (p-value=0.015) as shown in **Table 4.**

Table 1: Comparison of clinical parameters among patients with and without echocardiographic abnormalities.

Variables	Echocardiographic abnormalities n=43	No abnormalities n=82	p-value
Age	62.4 ± 14.3	58.51 ± 12.7	0.122
Gender			
Male	65.1% (28)	62.2% (51)	0.748
Female	34.9% (15)	57.8% (31)	
Moderate to Severe COVID-19	90.7% (39)	75.6% (62)	0.042
Ejection fraction%	55(30.0-55.0)	60(55-60)	0.0001
Mechanical ventilation for critical COVID-19	20.9% (9)	22% (18)	0.895
Mortality	30.2% (13)	11% (9)	0.007
Length of stay (days)	10.5 ± 6.9	9.3 ± 6.2	0.32

Table 2: Comparison of cardiac biomarkers among patients with and without echocardiographic changes.

Median (IQR)	Echocardiographic abnormalities n=43	No abnormalities n=82	p-value
D-dimer (Baseline) ng/ml	1.5(0.67-2.9)	0.65(0.325-1.95)	0.006
D-dimer (Peak) ng/ml	6.35(3.42-14.2)	1.4(0.80-4.85)	0.0001
Troponin (Baseline) ng/ml	0.05(0.00-0.25)	0.00(0.00-0.012)	0.0001
Troponin (Peak)	1.14(0.14-4.47)	0.02(0.00-0.10)	0.0001
CRP (Baseline) mg/ml	4.1(0.70-28.0)	5.8(0.95-50.5)	0.069
CRP (Peak) mg/ml	159(80.0-201.2)	122(57-182)	0.108
Pro-BNP levels	1114(155-6187.75)	569(206-1861.5)	0.108

Table 3: Correlation of cardiac biomarkers with LV function.

	Troponin	Peak CRP	Peak D-Dimer	Pro-BNP levels
Spearman's correlation coefficient for LVEF	-0.376	-0.238	-0.27	-0.281
P-value	<0.001	0.009	0.003	0.003

Table 4: Mortality in relation to echocardiographic parameters.

ECHOCARDIOGRAPHIC PARAMETERS	Total %(n)	Survivors %(n)	Non-survivors %(n)	Odds ratio (95% CI)	P value
Without pulmonary hypertension (PASP < 40 mm Hg)	82.4%(103)	86.4%(89)	13.6%(14)	3.63 (1.29-10.23)	0.015
With pulmonary hypertension (PASP >40 mm Hg)	17.6%(22)	63.6% (14)	36.4% (8)		
LV Systolic Function					
Normal	83.2%(104)	84.6%(88)	15.4%(16)	0.45 (0.15-1.34)	0.205
Impaired	16.8 %(21)	71.4%(15)	28.6%(6)		
Mildly reduced	4%(5)				
Moderately reduced	3.2%(4)				
Severely reduced	9.6%(12)				

Discussion

The incidence of echocardiographic abnormalities in patients with COVID-19 disease is variable. Carrizales-Sepúlveda et al, reported that Right Ventricular Dysfunction (RVD) was found to be present in 3.6% to 40% of COVID-19 patients while LV Dysfunction (LVD) ranged from 5.4% to 40.0% [18]. Similarly, our study has shown comparable results (RVD 4.0% and LVD 16.8%) Different studies worldwide **(Table 5)**, have reported variable results due to different study designs (retrospective vs prospective), heterogenous population, COVID-19's severity and healthcare resources [11,12,15,19-22].

Authors	*LV dysfunction*	*RV Dysfunction*
Dweck et al [11]	39%	33%
Jain et al [12]	34.70%	26.40%
Mahmoud-Elsayed et al [15]	11%	27%
Churchill et al [19]	27%	Not reported
Szekely et al [20]	10%	17%
WASE-COVID Study [21]	20%	30%

We found a weak inverse relationship between EF and different biomarkers including troponin, peak CRP, peak D-dimer, and NT-pro BNP levels. In comparison to our study, this inverse weak correlation between impaired LV function and high sensitivity troponin levels (hs-cTn) or NTproBNP levels were also reported by Jain et al [12] and Rath et al [14]. Left ventricular function and dimensions did not significantly differ between disease severity categories in a study by Szekely et al [20].

In a study by Pagnesi et al [23], the prevalence of pulmonary hypertension (PH) and RVD was reported to be 12.0% and 14.5% respectively, and the presence of PH was associated with a higher rate of in-hospital deaths or ICU admission (41.7 vs 8.5%, p<0.001). In parallel, our study has also shown significant pulmonary hypertension in patients with echocardiographic abnormalities that were more prevalent in our non-survivor population.

TTE resulted in changes in the management of around 33% of COVID-19 patients in a multicenter global evaluation of echocardiography in patients with COVID-19 [11] conversely this was lower (16.7%) in a study by Jain et al [12] and in our study as well (16.0%).

The WASE-COVID study [21] showed that age at presentation, previous lung disease, lactic dehydrogenase, LV longitudinal strain, and RV free-wall strain were independently associated with in-hospital mortality. In comparison, we have also observed higher mortality in patients with impaired LV systolic function and patients with overall echocardiographic abnormalities.

The strengths of our study are that it was conducted in the first-ever outbreak period of the disease in Pakistan, when the majority of the affected patients were admitted to the largest tertiary care hospital in our city, therefore it has highlighted the significance of doing echocardiographic assessment in patients with COVID-19 disease and also to limit the exam in critical patients so as to reduce health-care personnel's exposure of the disease.

There are also several limitations of the study. This was a single-center, retrospective study with a relatively smaller number of patients. There was no control group and possible selection bias as certain patients with poor echocardiographic windows were excluded. Echocardiograms were done at variable time intervals after admission and echocardiography protocols were not uniform. Cardiologists reporting the echocardiogram were not blinded and the follow-up echocardiogram data was not evaluated.

Conclusion

LV function assessment was the most common indication for TTE and was normal in the majority of the population. There was a weak inverse correlation of LV function with cardiac biomarkers. Overall mortality was higher in the patients with echocardiographic changes. The echocardiographic evaluation resulted in a change in the management of less than one-third of patients. Further larger studies are required as data on echocardiographic abnormalities in COVID19 patients in Pakistan is scarce.

Conflicts of interest: There are no conflicts of interest.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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