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Delayed Effect of COVID-19 Infection on Right Ventricular Function and Geometry

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Abstract:

Background: Coronavirus disease 2019 (COVID-19) has spread rapidly and triggered a terrible global pandemic that involves more than 200 countries/regions. This study aimed to detect subtle right ventricle (RV) dysfunction and structural changes in recovered patient from Covid -19 within 3 month of discharge using speckle tracking derived strain and conventional echo and to detect all predictors associated with RV dysfunction relevant to hospital outcome. **Methods:** This prospective observational cohort single center study included 200 patients post recovery from moderate to severe COVID 19 infection within the first three month after discharge who were admitted at Cardiology Specialized Hospital, Kobry El Kobba Medical Military Complex. Patients were sub-classified according to results of right ventricular free-wall longitudinal strain (RVFwLS): Group A: 172 patients with no RV affection, normal (≤ -20%). Group B: 28 patients with with RV affection, abnormal (> −20%). **Results:** RVfwLS, and RVGLS had significant p-value in predicting mortality post-COVID-19 infection. The area under curve (AUC) for RVfwLS was 0.634 (95% confidence interval (CI)=0.491-0.777; P=0.045) indicating acceptable discriminative ability. The AUC for right ventricular global longitudinal strain was 0.631 (95% CI=0.492-0.771; P=0.049) indicating acceptable discriminative ability. **Conclusion:** Early detection and management of RV dysfunction in this population may be crucial in preventing long-term cardiovascular complications. The findings of this study highlight the critical role of RV dysfunction as a predictor of mortality and poor outcomes in post-COVID-19 patients.

Keywords: Delayed Effect; Coronavirus disease 2019; Right Ventricular Function; Geometry.

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Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly and triggered a terrible global pandemic that involves more than 200 countries/regions. On 6 December 2020, there were more than 66.9 million confirmed cases and 1,534,954 deaths internationally [1].

Although the main target of the disease is respiratory tract; COVID-19 may affect all of the organ systems such as cardiovascular system. Micro thrombogenesis due to hypercoagulapathy, increased systemic inflammatory response, hypoxia, and hypotension are thought to play major role in the pathophysiology of cardiac involvement following severe acute respiratory syndrome (SARS)-COVID-19 Infection [2].

The right ventricle (RV) is vulnerable to a slight increase in pulmonary vascular resistance, making it more vulnerable to injury than the left ventricle [3], RV damage is associated with a higher incidence of myocardial damage in COVID-19 and generally predicts a worse prognosis [4]. RV involvement has been observed more commonly than left ventricular (LV) involvement in patients with COVID-19, with ~40% of patients experiencing RV dilatation and RV dysfunction [5, 6]

The mechanisms of RV damage may be due to increased RV afterload and decreased RV contractility caused by various factors, such as acute respiratory distress syndrome, pulmonary thrombosis, direct viral injury, hypoxia, inflammatory response and autoimmune injury. Timely and effective treatment is of vital importance to save patients' lives as well as improve prognosis. By illustrating the phenomenon. Of RV damage and its potential pathophysiological mechanisms, we will guide doctors to give timely medical treatments (e.g., anticoagulants, diuretics, cardiotonic) [7].

RV damage may be an association between myocardial damage and lung injury in COVID-19. Early assessment of RV geometry and function after discharge will be helpful in etiological determination and adjustment of treatment options [3]. Conventional echocardiographic parameters alone are not sensitive to early RV systolic dysfunction, and therefore, cannot be used for early diagnosis [8]

Two-dimensional speckle tracking echocardiography can more accurately evaluate myocardial function and detect subclinical cardiac functional impairment earlier than conventional echocardiography, which can measure LV global longitudinal strain (LVGLS), RV longitudinal strain (RVLS), RV free wall strain (RVFWS), and RV global strain (RVGS) [9].

Complex systemic inflammatory response may last long and affect ventricular functions. Several studies including COVID-19 patients in which right ventricular (RV) functions were evaluated by echocardiography in the early stages of the disease demonstrated that COVID-19 affects RV functions. However, there is no enough data about the long term effects of moderate to severe COVID-19 disease on RV function [2].

The purpose of this study was to detect subtle RV dysfunction and structural changes in recovered patient from Covid - 19 within 3 month of discharge using speckle tracking derived strain and conventional echo and to detect all predictors associated with RV dysfunction relevant to hospital outcome.

Patients and methods

This prospective observational cohort single center study included 200 patients post recovery from moderate to severe COVID 19 infections within the first three month after discharge who were admitted at Cardiology Specialized Hospital, Kobry El Kobba Medical Military Complex from June 2022 to June 2024.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study

was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University and Kobry El Kobba Medical Military Complex.

Inclusion criteria were documented COVID 19 adult cases with age range from 18 – 65 years with moderate to severe infection that needed hospital admission whether in a ward or ICU.

Exclusion criteria were patients with known RV dysfunction or pulmonary hypertension (HTN), previously diagnosed cardiac patients before COVID 19 infection i.e., previous heart failure, ischemic heart disease, previous percutaneous coronary intervention, coronary artery bypass grafting, with non-sinus rhythm before COVID 19 infection and with advanced kidney or liver disease.

Grouping: Patients were sub-classified according to results of RVFWLS: **Group A (n=172):** No RV affection, normal (≤ -20%). **Group B (n=28):** With RV affection, abnormal (> −20%).

A custom-made sheet was used to include all relevant data from the patients' records during hospital admission and treatment for COVID 19 infection. **All studied cases were subjected to the following: Full history taking, including [**Personal history (age, gender, occupation, and demographic details), respiratory symptoms, cardiovascular symptoms, past medical history: (HTN, coronary artery disease, heart failure), medications: (any antihypertensives, anticoagulants, or other cardiovascular medications), social history: (smoking, alcohol use, and exercise habits), clinical presentation on admission, cardiovascular risk including (HTN [(10)], obesity [(11)], diabetes mellitus (DM) [(12)], dyslipidemia [(13)], chronic kidney disease [(14))]. **Full clinical examination:** General examination including (measurement of weight, height, body mass index, temperature, systolic and diastolic blood pressure), vital signs including (blood pressure, heart rate, respiratory rate, and oxygen saturation) general appearance: (signs of distress, such as tachypnea, cyanosis, or diaphoresis), cardiovascular examination, respiratory examination, abdominal examination. **Routine laboratory investigations [**complete blood count: (hemoglobin (Hb) concentration, platelet count, white blood cells count, red blood cells count), renal function tests (urea and creatinine), liver function tests (alanine transaminase and aspartate aminotransferase), ferritin, polymerase chain reaction (PCR), cardiac biomarkers including (Troponin, N-terminal pro B-type natriuretic peptide (NT-proBNP), D-dimer), C-reactive protein (CRP), interleukifn-6, lipid profile (total cholesterol, high-density lipoproteins, low-density lipoprotein, and triglyceride), medical treatment received (chloroquine, antiviral, steroids, anticoagulation)]. **Radiology** including routine chest radiography.

Diagnosis of COVID 19 starting by identifying probable SARS-coronavirus 2 (CoV-2) infected patients and grading severity. Symptom-based criteria: any of (Fever (≥38°C or subjective fever), cough, shortness of breath or difficulty breathing, new loss of taste or smell myalgia or fatigue, sore throat, gastrointestinal symptoms (nausea, vomiting, diarrhea). **Radiologic criteria:** Chest X-ray or computed tomography scan showing bilateral ground-glass opacities or consolidations typical of COVID-19 pneumonia. **Confirmed case criteria:** Positive molecular testing (Real time (RT)-PCR) for SARS-CoV-2 from respiratory specimens (nasopharyngeal, throat swabs, or sputum)

Severity criteria (Used for trial stratification) including mild: No pneumonia and no oxygen requirement, moderate: Pneumonia without significant oxygen desaturation, severe: $SpO_2 \leq 94\%$ on room air, Respiratory rate ≥ 30 breaths per minute, lung infiltrates involving >50% of the lung field within 24-48 hours, critical: acute respiratory distress syndrome (ARDS) Respiratory failure

requiring mechanical ventilation Shock or multi-organ dysfunction.

According to the World Health Organization [15], patients who were matching the definition of probable SARS-CoV-2 infection underwent testing with molecular methods to scan for viruses. Throat and nasopharynx swab samples were collected from all patients in our study to extract SARS-CoV-2 RNA. Real-time reverse transcription polymerase chain reaction assay (RTPCR) molecular method was applied for RNA analysis of SARS-CoV-2 virus. RT-PCR assay was performed using the SARS-CoV-2 (2019-nCoV) qPCR Detection Kit (Bioeksen R&D Technologies Co Ltd, Istanbul, Turkey). Cases with SARS-CoV-2 RNA in RT-PCR method were accepted as COVID-19.

Two-dimensional echocardiography (2D-E)

Bedside transthoracic echocardiographic examinations were performed in all patients using the EPIQ 7C ultrasound system (Philips Medical Systems, Andover, Massachusetts). Two-dimensional and Doppler echocardiography was performed on the basis of the guidelines of the American Society of Echocardiography ([16]). All these echocardiographic examinations were performed by experienced two operators. Echocardiographic examinations were performed in left lateral decubitus position after resting for at least 15 min. All measurements were taken in three consecutive cycles, and average values were calculated. Parasternal long and short axis views and apical views were used as standard imaging windows. LV end-diastolic/end-systolic diameters were measured using M-mode with the parasternal long axis view and thereafter from apical four chamber and biplane window views were used to measure left ventricular end-diastolic and end-systolic volume.

Left ventricular ejection fraction (LVEF) was calculated from the apical window using the modified Simpson method. Left atrium diameter was determined from M-mode echocardiographic images using a leading-edge-to-leading-edge method, measuring the maximal distance between the posterior aortic root wall and the posterior left atrial wall at end-systole. Peak velocities of the early diastolic (E) and late diastolic (A) waves were measured at the point of mitral leaflet coaptation in the apical 4-chamber (A4C) views for the evaluation of diastolic functions. The peak velocities of early diastolic waves (septal e′ and lateral e′) were measured by PW tissue doppler imaging (TDI) from the lateral and septal mitral annulus. E/e′ (lateral) ratio was calculated.

RV diameters were measured at RV mid-region and basal region from apical four-chamber view. Percentage right ventricular fractional area change (RV-FAC) was calculated by dividing the difference in RV area between the end diastolic and end-systolic phases by end-diastolic RV area. Tricuspid annular plane systolic excursion (TAPSE) is defined as the distance traveled between end-diastole and end-systole at the lateral corner of the tricuspid annulus. Systolic pulmonary artery pressure was calculated as the sum of right atrial pressure value obtained by Bernoulli's equation from tricuspid valve pressure gradient and caval respiratory index. Calculation of the RV myocardial performance index was assessed by PW TDI. To measure RV S', RV-focused view is used with tissue doppler region of interest placed at the lateral corner of the tricuspid annulus acquired at high frame rate. The velocity S' is read as the highest systolic velocity. By PW TDI the encompasses isovolumetric contraction time, ejection time (ET), and isovolumetric relaxation time. Intraobserver and interobserver variations for echocardiographic measurements were less than 4%.

Assessment of right ventricle speckle tracking echocardiography (RV-STE)

While performing RV-2D strain imaging; the patient's heart rhythm was monitored with echocardiography, 2D video data were recorded from the modified A4C view, and RV-focused images including at least three cardiac cycles with regular ECG signals were obtained in the tissue velocity imaging mode. The of-line analysis of recorded image sequences and signals was performed using the commercially software (QLAB-CMQ, Philips Healthcare, Andover, Massachusetts) on a computer workstation. After defining three reference landmarks (RV apex, medial and lateral tricuspid annulus), the software automatically traced the endocardial and epicardial borders in the modified A4C view. Tracking points were adjusted manually if necessary, and 2D longitudinal strain and strain rate curves were obtained for each myocardial segment. Peak negative longitudinal systolic strain variables were derived from these curves. RV global longitudinal strain (RVGLS) and RVFWLS values were measured according to the current guidelines [17].

Cardiac biomarkers: High sensitivity troponin (I or T depending on assay used at each site) and NT-proBNP were measured in all patients on the day of echocardiography. Samples were processed alongside routine clinical samples in each host site, and therefore subject to routine laboratory quality assurance processes. Abnormal values were defined for NT-proBNP (>300ng/ml) and Troponin (TnT ≥15 ng/L or Tnl ≥34 ng/L for males; ≥16 ng/L for females).

Functional capacity: The Duke Activity Status Index was used to assess subjective functional capacity, measured as estimated metabolic equivalents (METS) [18]. This self-administered questionnaire has previously been correlated with peak oxygen uptake and outcome, and we identified the test as abnormal if the score was <85% of age- and sex-defined METS. The 6-minute walk distance was performed in line with the American Thoracic Society guidelines and was identified as abnormal if it was <85% of age-specific normal findings [19].

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Sample size

200 patients post recovery from moderate to severe COVID 19 infection within the first three month after discharge.

Statistical analysis

Data management and statistical analysis were done using SPSS version 27 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Kolmogorov–Smirnov test. Quantitative data were summarized as mean and standard deviation. Categorical data were summarized as numbers and percentages. Quantitative data were compared between any two unpaired groups using Mann-Whitney U test or independent sample t test according to normality. Categorical data were compared using the Chi-square, and Fisher exact. Cox regression was used to detect predictors of RV dysfunction and mortalities. Receiver operating characteristic (ROC) analysis was done to RVfwLS, TAPSE, RVSP and fractional area change (FAC), RVGLS to diagnose occurrence of mortalities. The areas under the curve with 95% confidence intervals, and diagnostic indices were calculated. All statistical tests were two-sided. *P* values less than or equal to 0.05 were considered significant.

Results

The males represented the highest proportion in patients with no RV affection (62.8%) however females with more dominant in RV affection group (53.6%).47 (27.3) out of 172 patients of no RV affection group suffered from DM and 19 (67.9) out of 28 patients of RV affection suffered from it and the relation was significant (P<0.001). HTN was found in 60 (34.9%) of no RV affection group and 9 (32.1%) of RV affection group and the observed difference was of no significant value. Significantly, fever was

more prominent in patients who developed RV affection (78.6%) compared with patients without RV affection (56.4%). Similarly, Chest pain was more prominent in patients who developed RV affection (53.6%) compared with patients without RV affection (29.1%) and the relation was significant (P=0.010). No significant difference was detected between both groups regarding prevalence of other COVID symptoms including cough, Athenia, myalgia, anorexia, dyspnea, diarrhea, sore throat. The mean Hb level was significantly higher among no RV affection group (13.5±1.1) compared with patients with RV affection (12.9±1.0; p=0.020). On contrary, D-dimer was significantly high among patients with RV affection (85.7%) compared with no RV affection group who tended to develop normal D- dimer in higher rate. CRP was significantly higher among RV affection group (60.7±32.0) compared with patients with no RV affection (45.6±33.8; p=0.012). Moreover, there was a significant difference between both groups regarding ferritin level (p=0.004). No significant difference between the two groups regarding total leucocytic count, platelets cell count, or lymphocytes. (**Table 1)**

None of the total participants reported taking choloroquine at the time of data collection. Patients with RV affection were significantly more brone to take antiviral, steroids, and anticoagulation (85.7%, 85.7%, 85.7% respectively) compared with no RV affection group (63.4%, 52.3%, 40.7% respectively). No significant difference between both groups regarding ECG changes except for QT duration whereas the mean duration was higher among RV affection group (420.6±26.9) compared with no RV affection group. (**Table 2)**

IVC was significantly higher among patients with RV affection (1.8±0.3) compared with no RV affection group (1.5±0.4; p=0.026). On contrary, Emsec, EDT, Lateral e', TAPSE, FAC and Tricusid s were significantly lower among patients with RV affection compared with no RV affection group. (**Table 3)**

LVGLS and RVGLS was significantly lower in patients with RV affection compared with no RV affection group. 28.6% of patients with RV affection had died within the follow-up compared with only 7.6% of normal group and the relation was of statistically significant value (p<0.001). (**Table 4)**

Univariate analysis demonstrated that abnormal RVFWLS is associated with higher mortality (log rank = 0.006). The mean survival time for normal RV group was 43.6, while it was 40.7 days for abnormal group. (Figure **1)**

Taking in consideration follow-up time, having abnormal RVFWLS (> −20%) was associated with 3.254 time increase risk of occurrence of mortality (95% CI=1.318-8.036; *P*=0.011). Also, one year increase was also associated with 1.104 increase risk of occurrence of mortality (95% CI=1.057-1.154; *P*<0.001). Taking in consideration follow-up time, it had been found that one year increase was associated with 1.04 increase risk of occurrence of RV dysfunction (95% CI=11.01-1.07; *P*=0.007). Moreover, being diabetic was associated with 5.61-time increased risk of developing RV dysfunction (95%CI=2.37-13.28; *P*<0.001). (**Figure 2)**

All of RVfwLS, TAPSE, RVSP and FAC, RVGLS were tested to assess its diagnostic ability in predicting mortality post-COVID-19 infection, however only RVfwLS, and RVGLS had significant p-value. The AUC for RVfwLS was 0.634 (95% CI=0.491-0.777; *P*=0.045) indicating acceptable discriminative ability. The AUC for RVGLS was 0.631 (95% CI=0.492-0.771; *P*=0.049) indicating acceptable discriminative ability. (**Figure 3)**

Table 1: Demographics, clinical history, risk factors and lab findings of the studied patients according to RVFWLS

Parameters			RVFWLS		Total participants n=200	p-value
			No RV affection (≤ -20%) n=172, 86.0%	With RV affection (> −20%) n=28, 14.0%		
Age (years)		**Mean ± SD**	41.7±14.4	49.7±11.5	42.8±14.3	**0.006*** ⊦
		Range (Min-Max)	20.0-70	37.0-68.0	20.0-71.0	
Gender	**Males**	**n (%)**	108 (62.8)	13 (46.4)	121 (60.5)	0.100 ⊦⊦
	Females	**n (%)**	64 (37.2)	15 (53.6)	79 (39.5)	
Clinical history and risk factors	**DM**	**n (%)**	47 (27.3)	19 (67.9)	66 (33.0)	**<0.001*** ⊦
	HTN	**n (%)**	60 (34.9)	9 (32.1)	69 (34.5)	0.777 ⊦
	Fever	**n (%)**	97 (56.4)	22 (78.6)	119 (59.5)	**0.027*** ⊦
	Cough	**n (%)**	67 (39.0)	12 (42.9)	79 (39.5)	0.835 ⊦
	Athenia	**n (%)**	40 (23.3)	3 (10.7)	43 (21.5)	0.134 ⊦
	Myalgia	**n (%)**	51 (29.7)	6 (21.4)	57 (28.5)	0.371 ⊦
	Anorexia	**n (%)**	25 (14.5)	6 (21.4)	31 (15.5)	0.379 ⊦⊦
	Dyspnea	**n (%)**	72 (41.9)	15 (53.6)	87 (43.5)	0.246 ⊦
	Chest pain	**n (%)**	50 (29.1)	15 (53.6)	65 (32.5)	**0.010*** ⊦
	Diarrhea	**n (%)**	34 (19.8)	6 (21.4)	40 (20.0)	0.839 ⊦
	Sore throat	**n (%)**	99 (57.6)	18 (64.3)	117 (58.5)	0.542 ⊦
Lab findings	**Hb**	**Mean ± SD**	13.5±1.1	12.9±1.0	13.4±1.1	**0.020*** ⊦
		Range	10.6-15.8	10.9-14.0	10.6-15.8	
	TLC	**Mean ± SD**	8.3±2.5	9.5±3.0	8.5±2.6	0.084 ⊦
		Range	3.1-14.6	5.4-13.2	3.1-14.6	
	PLT	**Mean ± SD**	279.0±67.8	298.1±38.3	281.6±64.7	0.061 ⊦
		Range	153.0-412.0	255.0-397.0	153.0-412.0	
	lymphocytes	**Mean ± SD**	2.0±1.1	2.4±1.3	2.1±1.1	0.108 ⊦
		Range	0.7-5.1	0.5-4.8	0.5-5.1	
	D dimer (High)	**no (%)**	79 (45.9)	24 (85.7)	103 (51.5)	**<0.001*** ⊦⊦
	CRP	**Mean ± SD**	45.6±33.8	60.7±32.0	47.7±33.9	**0.012*** ⊦
		Range	4.0-123.0	7.0-112.0	4.0-123.0	
	Ferritin	**Mean ± SD**	651.4±240.1	803.0±150.9	672.9±235.8	**0.004*** ⊦
		Range	49.0-1081.0	612.0-1140.0	49.0-1140.0	

RVFWLS: Right Ventricular free-wall longitudinal strain, Hb: Hemoglobin level, TLC: Total leucocytic count, PTL: Platelets cell count, CRP: C-reactive protein, ⊦ Mann-Whitney U test, ⊦⊦Chi-square test, *Indicates significant p-value at level of significance ≤0.05

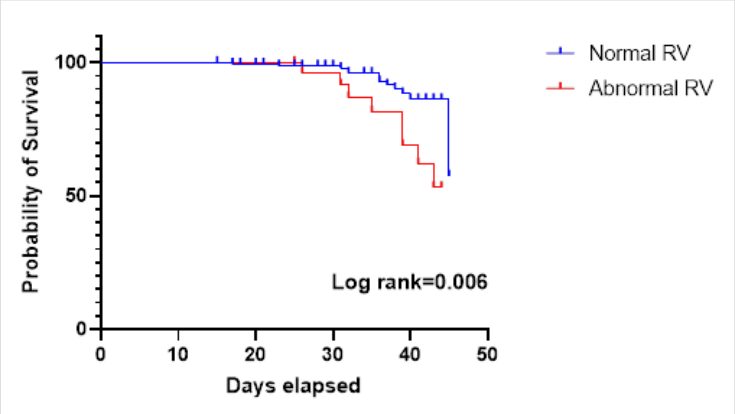
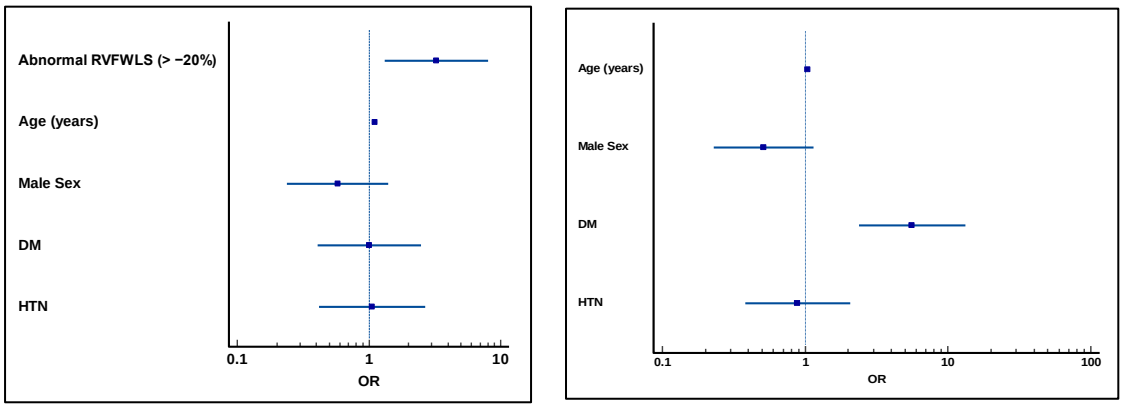


Figure 1: Kaplan–Meier and log rank analysis of patients with normal RVFWLS (≤ −20%) (Blue) compared to abnormal RVFWLS (> −20%) (Red). Kaplan–Meier plot displays cumulative survival in the group

Table 2: Medication intake, ECG changes among the studied patients stratified by RVFWLS results

Variables			RVFWLS		Total	p-value
			No RV affection (≤ -20%) n=172, 86.0%	With RV affection (> −20%) n=28, 14.0%	participants n=200	
chloroquine			0 (0.0)	0 (0.0)	0 (0.0)	---
antiviral			109 (63.4)	24 (85.7)	133 (66.5)	**0.020*** ⊦
steroids			90 (52.3)	24 (85.7)	114 (57.0)	**<0.001*** ⊦
anticoagulation			70 (40.7)	24 (85.7)	94 (47.0)	**<0.001*** ⊦
ECG changes	**Rhythm**	**Non sinus (AF)**	172 (100.0)	28 (100.0)	200 (100.0)	--
	PR duration		158.1±20.3	164.1±19.6	158.9±20.2	0.167⊦
			120.0-193.0	129.0-188.0	120.0-193.0	
	QT duration		408.3±15.1	420.6±26.9	410.1±17.7	**0.043*** ⊦
			360.0-440.0	395.0-490.0	360.0-490.0	
	QRS duration		97.1±8.6	96.0±7.8	97.0±8.5	0.650⊦
			80.0-116.0	83.0-110.0	80.0-116.0	
	ST	**Normal**	163 (94.8)	25 (89.3)	188 (94.0)	0.381 ⊦⊦
		Abnormal	9 (5.2)	3 (10.7)	12 (6.0)	
	T wave	**Normal**	166 (96.5)	28 (100.0)	194 (97.0)	0.598⊦⊦
		Abnormal	6 (3.5)	0 (0.0)	6 (3.0)	

Data presents as mean ± SD, range or frequency (%) , AF: Atrial fibrillation, PR: pulse rate, ⊦Chi-square test, ⊦⊦ Fisher exact test, RVFWLS: right ventricular free-wall longitudinal strain *Significant p value



(A) **(B)**

Figure 2: (A): Forest plot of predictors of mortality, (B): Forest plot of predictors of RV dysfunction

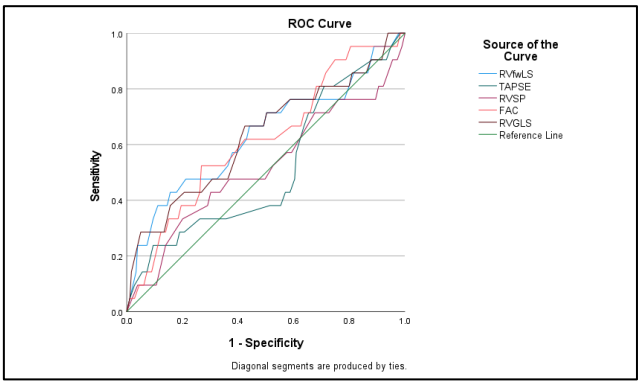


Figure 3: Roc curve for RVfwLS, TAPSE, RVSP and FAC, RVGLS for predicting mortalities

Table 3: Echo parameters among the studied patients stratified by RVFWLS results

Variables		RVFWLS		Total participants n=200	p-value
		No RV affection (≤ -20%) n=172, 86.0%	With RV affection (> −20%) n=28, 14.0%		
LViDd	**Mean ±SD**	47.3±2.4	47.9±2.4	47.3±2.4	0.245 ⊦
	Range	43.0-51.6	45.0-51.0	43.0-51.6	
LVIDs	**Mean ±SD**	29.8±2.0	30.6±3.2	29.9±2.2	0.393 ⊦
	Range	26.0-37.0	27.0-37.0	26.0-37.0	
IVSd	**Mean ±SD**	7.7±1.6	7.9±0.9	7.8±1.6	0.899 ⊦
	Range	0.7-10.3	6.8-9.6	0.7-10.3	
LVPWd	**Mean ±SD**	7.6±1.5	7.8±0.9	7.6±1.4	0.396 ⊦
	Range	0.8-10.0	6.2-9.2	0.8-10.0	
LVEF	**Mean ±SD**	66.1±3.7	65.3±5.0	66.0±3.9	0.704 ⊦
	Range	52.2-71.7	53.5-71.1	52.2-71.7	
IVC	**Mean ±SD**	1.5±0.4	1.8±0.3	1.6±0.4	**0.026*** ⊦
	Range	0.6-2.3	1.3-2.2	0.6-2.3	
LAVi (ml/m^2)	**Mean ±SD**	19.8±3.8	20.7±3.2	20.0±3.7	0.167 ⊦
	Range	12.2-29.4	16.7-25.0	12.2-29.4	
E (msec)	**Mean ±SD**	79.1±20.3	65.1±16.3	77.1±20.3	**<0.001*** ⊦
	Range	43.0-126.0	44.0-94.0	43.0-126.0	
A (msec)	**Mean ±SD**	65.4±15.2	63.3±14.9	65.1±15.1	0.683 ⊦
	Range	32.0-98.0	33.0-84.0	32.0-98.0	
EA	**Mean ±SD**	1.3±0.4	1.1±0.3	1.2±0.4	0.086 ⊦
	Range	0.6-2.2	0.7-1.5	0.6-2.2	
EDT	**Mean ±SD**	166.6±36.2	134.1±31.8	162.0±37.3	**<0.001*** ⊦
	Range	96.0-269.0	83.0-186.0	83.0-269.0	
SeptaL e'	**Mean ±SD**	10.8±2.7	9.6±2.9	10.6±2.8	0.052 ⊦
	Range	5.0-15.4	4.0-14.0	4.0-15.4	
Lateral e'	**Mean ±SD**	15.9±3.7	13.4±2.9	15.6±3.7	**<0.001*** ⊦
	Range	8.0-21.5	9.1-18.0	8.0-21.5	
E e~	**Mean ±SD**	5.9±1.3	5.7±1.0	5.9±1.3	0.506 ⊦
	Range	0.8-9.2	4.1-7.4	0.8-9.2	
RVSP	**Mean ±SD**	16.6±7.6	20.3±12.0	17.1±8.4	0.176 ⊦
	Range	6.0-34.0	8.0-49.0	6.0-49.0	
TAPSE	**Mean ±SD**	21.5±2.5	19.1±3.9	21.1±2.8	**0.007*** ⊦
	Range	15.0-26.0	11.2-25.0	11.2-26.0	
FAC	**Mean ±SD**	48.3±6.1	42.9±5.5	47.5±6.3	**<0.001*** ⊦
	Range	34.2-64.5	33.0-51.0	33.0-64.5	
Tricusid s	**Mean ±SD**	13.3±1.5	12.5±1.6	13.2±1.5	**0.009*** ⊦
	Range	11.0-16.6	10.5-15.7	10.5-16.6	

LViDd: Left ventricular internal diastolic diameter, LVIDs: Left ventricular internal diameter end systole, IVSd: interventricular septum thickness in diastole, LVPWd: Left Ventricular Posterior Wall end-diastole, LVEF: Left ventricular ejection fraction, IVC: inferior vena cava, LAVi: LA volume index, E:early diastolic, A:late diastolic, SeptaL e, Lateral e': peak velocities of early diastolic waves, EDT: E-wave deceleration time, RVSP: right ventricular systolic pressure, TAPSE: Tricuspid annular plane systolic excursion, FAC: fractional area change, RVFWLS: right ventricular free-wall longitudinal strain, *: statistically significant as P value <0.05, ⊦ Mann-Whitney U test

Table 4: Speckle tracking echocardiography parameters stratified by RVFWLS results and Comparison between patients with and without RV affection regarding mortalities

Variables		RVFWLS		Total participants n=200	p-value
		No RV affection (≤ -20%) n=172, 86.0%	With RV affection (> −20%) n=28, 14.0%		
LVGLS	**Mean ± SD**	22.1±2.1	20.2±1.8	21.9±2.1	**<0.001***ŧ
	Range (Min-Max)	19.1-29.2	17.0-22.6	17.0-29.2	
LVGCS	**Mean ± SD**	23.6±1.2	22.9±1.3	23.5±1.2	0.056ŧ
	Range (Min-Max)	21.5-26.5	20.7-25.0	20.7-26.5	
RVGLS	**Mean ± SD**	24.8±3.8	18.9±1.1	24.0±4.1	**<0.001***ŧ
	Range (Min-Max)	18.6-32.9	17.1-20.9	17.1-32.9	
Mortality	**no (%)**	13 (7.6)	8 (28.6)	21 (10.5)	**<0.001***ŧ

RVFWLS: right ventricular free-wall longitudinal strain, LVGLS= Left Ventricular Longitudinal Global Strain, LVGCS=left ventricular global circumferential strain, RVGLS=Right Ventricular Longitudinal Global Strain, ŧ Mann-Whitney U test*: statistically significant as P value <0.05

Discussion

RV dysfunction is a common echocardiographic feature in COVID-19 infection and is associated with increased mortality [20].

Our study revealed that RV affection was found in 14.0% (28 out of 200 studied patients) based on results of RVFWLS.

Also, McErlane et al. [21], revealed that 27 patients out of 94 (28.7%) had RV dysfunction.

Much higher than our current study, Sanchez et al. [22], found that the prevalence of RV dysfunction among the studied participants was 69.0% (80 patients out of 116).

Multiple studies of severe COVID-19 estimate the prevalence of RV dysfunction by echocardiography to be between 14% and 72% [23, 24]. This is similar to the previously reported prevalence of RV dysfunction in non–COVID-19 ARDS (22–55%) [25].

This variation between studies can be attributed to many factors; first, it could be due to the variation in RV dysfunction case definition across different studies. For instance, our current studies considered RV affection if the patient had RVFWLS > −20%.

In the recent study conducted by Sanchez et al. [5], defined RV dysfunction as RVFAC < 35%, TAPSE < 17 mm, or RVFWS < 20.0%, and dilatation, as RV basal dimension > 41 mm or RV end-diastolic area > 25 cm^2.

McErlane et al. [21], used the same case definition as this current study, whereas patients were considered having RV dysfunction if the RVFWLS >-20%.

Another explanation of variation between studies could be attributed to the timing of data collection, which would be affected by the circulating COVID variant at that time. Ghantous et al. [26], found that, in patients with Omicron, RV function is impaired to a lower extent compared with the wild-type variant.

Omar et al. [27], claimed that RV dysfunction continues to occur in all strains of the SARS-CoV-2 virus, however, the mortality risk decreased from wave to wave.

Our study revealed a significant association between older age and the presence of RV dysfunction. Patients with RV dysfunction had a mean age of 49.7 years, significantly higher than the 41.7 years observed in those without RV dysfunction (p=0.006).

This finding aligns with several studies that have highlighted the vulnerability of older adults to cardiovascular complications following COVID-19. For instance, a study by Sanchez et al. [5], reported that older patients were more likely to develop RV dysfunction, possibly

due to underlying comorbidities and age-related cardiovascular changes. The age-related decline in cardiovascular reserve, combined with the pro-inflammatory state induced by COVID-19, could exacerbate RV strain in older individuals.

On contrary, Beyls et al. [20], reported non-significant difference between patients with and without RV dysfunction cording to age (p=0.130) and even the of patients with RV affection (median=59 years) was slightly younger that patients without RV affection (median 63 years).

The geriatric population is especially vulnerable to COVID-19 and its potential complications [28]. Moreover, elderly is more vulnerable to cardiovascular complications. As a matter of fact, elderly is more vulnerable to different health problems [29].

Interestingly, females were more likely to develop RV dysfunction than males in our cohort (53.6% vs. 37.2%, p=0.100). While this difference did not reach statistical significance, it points to a trend that has been observed in other studies.

Some research, such as the study by Bielecka-Dabrowa et al. [30], suggests that women may be more susceptible to post-COVID-19 complications, potentially due to hormonal differences that influence the cardiovascular response to stress.

Estrogen has protective effects on the heart [31], but in the context of COVID-19, it may also modulate the immune response in a way that predisposes women to cardiovascular issues. However, this finding remains controversial, as many studies have reported higher rates of severe COVID-19 and cardiovascular complications in men [20, 21].

Our study identified a significant association between DM and RV dysfunction, with 67.9% of patients with RV dysfunction having DM compared to 27.3% in those without RV dysfunction (p<0.001).

This strong association is supported by a growing body of literatures that found that DM is a major risk factor for cardiovascular complications in COVID-19 patients [32, 33] likely due to the chronic inflammation and endothelial dysfunction seen in diabetic individuals, which may be exacerbated by the viral infection.

HTN, another commonly reported risk factor for cardiovascular disease, showed no significant difference between the groups in our study (p=0.777).

This contrasts with studies such as Khairy et al. [34], which reported a higher prevalence of HTN in patients with severe COVID-19 and subsequent cardiovascular complications and that HTN increases COVID-19 severity due to underlying endothelial dysfunctions and coagulopathy and also that COVID was shown to be a predisposing factor for occurrence of HTN as indicated by Krishnakumar et al. [35], that 10%–30% newly diagnosed HTN in patients recovered from COVID-19.

The lack of association in our study may be due to the relatively small sample size of the RV dysfunction group (n=28) or the fact that many hypertensive patients receive treatments that could mitigate the cardiovascular impact of COVID-19, such as ACE inhibitors or angiotensin II receptor blockers.

Fever and chest pain were significantly more common in patients with RV dysfunction compared to those without (p=0.027 and p=0.010, respectively). Fever is often associated with systemic inflammation, and in COVID-19, this inflammation can extend to the cardiovascular system, leading to myocarditis or pericarditis, which may affect the function of the RV.

Cann et al. [36] reported that fever was linked to more severe systemic inflammation in COVID-19 patients, which may explain its association with RV dysfunction in our cohort.

Chest pain, particularly of a pleuritic nature, could be indicative of pericarditis or pulmonary embolism both of which have been reported as complications of COVID-19.and are known to affect RV function [37-39].

Other COVID-19-related symptoms, such as cough, dyspnea, and myalgia, did not show significant differences between the groups, suggesting that their presence alone may not be predictive of RV dysfunction. However, as a matter of fact, the common symptoms of COVID-19 are fever, cough, shortness of breath or dyspnea, muscle aches, diarrhea, loss of smell and taste, and fatigue in most patients [40].

Several laboratory findings were significantly associated with RV dysfunction in our study. Hb levels were lower in patients with RV dysfunction (12.9±1.0 vs. 13.5±1.1, p=0.020).

Anemia has been linked to worse outcomes in COVID-19, possibly due to its impact on oxygen delivery to tissues, including the heart [41, 42].

A study by Faghih et al. [43] found that lower Hb levels were independently associated with adverse cardiac outcomes in COVID-19 patients.

D-dimer levels were significantly higher in patients with RV dysfunction ($p<0.001$), which is consistent with the literature.

Esmailian et al. [44] found that elevated D-dimer levels in COVID-19 patients were predictive of both thrombotic events and RV strain.

CRP and ferritin, markers of inflammation, were also significantly elevated in patients with RV dysfunction (p=0.012 and p=0.004, respectively).

These findings are consistent with Ruan et al. [45] who reported that higher levels of inflammatory markers were associated with cardiac injury in COVID-19 patients.

The systemic inflammatory response in severe COVID-19 can lead to endothelial dysfunction, hypercoagulability, and direct myocardial injury, all of which could contribute to RV dysfunction.

Patients with RV dysfunction were significantly more likely to have been treated with antivirals, steroids, and anticoagulants than those without RV dysfunction. This finding reflects the more severe clinical course of those with RV dysfunction, as these medications are typically reserved for patients at higher risk of complications.

RECOVERY trial findings, Horby et al. [46] demonstrated that steroids, particularly dexamethasone, reduce mortality in severe COVID-19, which could explain their higher use in patients with RV dysfunction**.**

The use of anticoagulants is consistent with the high D-dimer levels observed in this group, as anticoagulation is often initiated to prevent thromboembolic events in patients with elevated D-dimer.

The only significant ECG difference between the groups was the QT duration, which was longer in the RV dysfunction group (p=0.043). Prolonged QT can be a marker of myocardial injury and arrhythmogenic risk, which has been reported in COVID-19 patients [47].

Many literatures suggested that systemic inflammation in COVID-19 can prolong the QT interval, potentially increasing the risk of arrhythmias [48].

The lack of significant differences in other ECG parameters may be due to the relatively mild nature of RV dysfunction in our cohort, as more severe dysfunction may result in more pronounced ECG changes.

RV dysfunction was associated with several echocardiographic abnormalities. Inferior vena cava (IVC) diameter was significantly larger in patients with RV dysfunction (p=0.026), indicating increased RV pressure and volume overload, which could be a result of pulmonary HTN or RV failure.

This finding is consistent with studies by Barman et al. [49] which showed that increased IVC diameter was a common feature of RV dysfunction in COVID-19 patients.

On the other hand, markers of RV function such as TAPSE and fractional area change (FAC) were significantly lower in patients with RV dysfunction. This is expected, as both TAPSE and FAC are well-established markers of RV systolic function.

Szekely et al. [50] found that reduced TAPSE and FAC were common in post-COVID-19 patients with RV dysfunction, likely due to the combined effects of direct myocardial injury and increased pulmonary vascular resistance.

The findings of our study are largely consistent with those reported in other cohorts of post-COVID-19 patients. However, some differences were observed. For example, while several studies have reported higher rates of ECG abnormalities, particularly arrhythmias, in patients with RV dysfunction, we did not observe significant differences in most ECG parameters. This could be due to differences in the severity of illness in our cohort compared to other studies, as well as the relatively short follow-up period of three months. Longer follow-up may reveal more pronounced cardiac abnormalities.

The study demonstrated that both LVGLS and RVGLS were significantly lower in patients with RV dysfunction compared to those without. Specifically, the mean LVGLS was - 20.2 ±1.8 in the RV dysfunction group compared to - 22.1±2.1 in the no-RV dysfunction group ($p<0.001$), while RVGLS was -18.9±1.1 versus -24.8±3.8, respectively ($p<0.001$).

These findings are consistent with previous studies that have established the utility of STE in detecting subclinical cardiac dysfunction in COVID-19 patients. Tryfou et al. [51] found that in patients with post-COVID myocardial injury, both LVGLS and RVGLS were significantly reduced, indicating that COVID-19 could lead to a decline in both left and RV function**.**

RVGLS, in particular, has been shown to be a sensitive indicator of RV dysfunction, which might not be apparent using conventional echocardiographic parameters alone.

The lower LVGLS in patients with RV dysfunction could be indicative of global cardiac involvement, with the RV dysfunction possibly acting as a marker for more widespread myocardial damage.

This is supported by studies such as Szekely et al. [50] which showed that a significant number of COVID-19 patients exhibited biventricular strain abnormalities, even in those without overt clinical signs of heart failure.

The mechanism behind this could be multifactorial, involving direct viral invasion of cardiomyocytes, cytokine-mediated myocardial injury, and the development of acute cor pulmonale due to COVID-19-associated pulmonary complications.

One of the most striking findings of this study is the relationship between RV dysfunction and mortality. The study found that 28.6% of patients with RV dysfunction died within the follow-up period, compared to only 7.6% of those without RV dysfunction ($p<0.001$). This significant association identifies RV dysfunction as a crucial predictor of poor prognosis in post-COVID-19 patients.

This finding aligns with several studies that have demonstrated the prognostic importance of RV function in COVID-19. In previous literatures, RV dysfunction was independently associated with increased in-hospital mortality in COVID-19 patients [20, 21].

The increased mortality in patients with RV dysfunction may be due to several factors. First, COVID-19 is associated with an increased risk of thromboembolic events, such as pulmonary embolism, which can acutely strain the RV. Second, the cytokine storm and widespread endothelial injury seen in severe COVID-19 can lead to diffuse myocardial inflammation, which disproportionately affects the RV due to its thinner wall and higher sensitivity to pressure overload. Finally, long-term pulmonary sequelae, such as lung fibrosis, can result in chronic RV strain and failure.

The survival analysis further demonstrated that patients with RV dysfunction had a significantly shorter mean survival time

(40.7 days) compared to those with normal RV function (43.6 days; log rank = 0.006). This finding reinforces the critical role of RV function in determining survival outcomes in post-COVID-19 patients.

Several studies have reported similar findings. Evrard et al. [52] using echocardiographic data, found that RV dysfunction was common in patients with severe COVID-19 and was associated with higher mortality and shorter survival times. The mechanism underlying this association may involve both acute and chronic pulmonary complications post-COVID-19, including persistent pulmonary HTN and RV failure, which lead to decreased cardiac output, poor perfusion, and multi-organ dysfunction.

ROC analysis revealed that both RVFWLS and RVGLS had significant discriminative ability in predicting mortality, with AUC values of 0.634 and 0.631, respectively (*p*=0.045 and p=0.049). These findings indicate that RV strain parameters are valuable tools for early identification of patients at higher risk of death post-COVID-19.

Previous studies have supported the role of RV strain as a prognostic marker in COVID-19 patients. Ji et al**.** and Li et al. [53, 54] showed that RVFWLS and RVGLS were independent predictors of mortality in hospitalized COVID-19 patients, with RV strain abnormalities providing incremental prognostic information beyond traditional echocardiographic parameters.

The relatively modest AUC values in our study suggest that while RV strain is a useful tool for predicting mortality, it should be used in conjunction with other clinical and echocardiographic parameters to enhance predictive accuracy.

The limitation of the study were this study is single center cross-sectional, only included patients who were admitted to the hospital's cardiology department during the post-recovery period, which may introduce selection bias, patients who were asymptomatic or had less severe COVID-19 and did not require hospitalization may have different cardiovascular outcomes, and their exclusion may skew the findings toward those with more severe disease or cardiovascular comorbidities and although the study followed patients for up to three months after hospital discharge, this may not be sufficient to fully capture the long-term cardiovascular effects of COVID-19, particularly the progression of RV dysfunction or the development of heart failure

Conclusion

Our study highlights the significant burden of RV dysfunction in post-COVID-19 patients, particularly among older adults, females, and those with comorbidities such as diabetes. The association of RV dysfunction with elevated D-dimer levels and inflammatory markers underscores the multifactorial nature of cardiac involvement in COVID-19, involving both thromboembolic and inflammatory mechanisms. Early detection and management of RV dysfunction in this population may be crucial in preventing long-term cardiovascular complications. The findings of this study highlight the critical role of RV dysfunction as a predictor of mortality and poor outcomes in post-COVID-19 patients. Speckle tracking-derived strain parameters, particularly RVFWLS and RVGLS, were shown to be sensitive indicators of RV dysfunction and were significantly associated with increased mortality. Our study adds to the growing body of evidence that COVID-19 can have lasting effects on the cardiovascular system, even after recovery from the acute phase of illness. Early identification of patients at risk for RV dysfunction and targeted interventions to improve RV function may help reduce mortality and improve long-term outcomes in this vulnerable population.

Therefore, longer-term follow-up studies are needed to assess the persistence or resolution of RV dysfunction and its

impact on long-term morbidity and mortality. While this study adds valuable information regarding the cardiovascular sequelae of COVID-19, particularly RV dysfunction, these limitations should be considered when interpreting the results.

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Conflicts of interest

No conflicts of interest

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