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Right Ventricular Abnormalities in Hospitalized Patients with Severe Covid-19 Infection

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Abstract

Background: Previous studies have demonstrated that COVID 19 is associated with significant right ventricular dilatation (RV) and systolic dysfunction.

Aim of Study: To evaluate the prevalence of right ventricular dilatation and enlargement and impaired pumping function among patients with acute Covid-19 infection and its relationship with in-hospital outcome.

Patients and Methods: In this study, 90 adult patients with acute severe COVID-19 infection who were admitted consecutively to ELMOKATTAM Health Insurance Hospital between August 2020 and February 2021 were included. All cases had full history taking, clinical, laboratory and echocardiography examinations, including measurement of right ventricular dimension and systolic function using tricuspid annular plane systolic excursion (TAPSE).

Results: RV abnormalities were found in 27 patients out of 90 (30%) with RV dilatation as the most common (25 patients, 27.8%), followed by RV systolic dysfunction (10 patients, 11.1%). RV abnormalities were associated with more severe lung disease based on CT chest severity score. Also, RV abnormalities was associated with less oxygen saturation, more use of mechanical ventilation and vasopressors. Cases with RV abnormalities showed higher levels of D-dimer, ferritin, troponin, CK-MB, serum creatinine and total leucocytic count. By employing multi-variate logistic regression analysis, RV dilatation revealed independent association with mortality during hospitalization (OR: 6.13, CI: 1.368 - 27.469, *p*: 0.018) along with total leucocytic count and oxygen saturation.

Conclusion: RV enlargement & systolic dysfunction was observed within 30% and 11% of cases hospitalized with severe COVID-19 infection, respectively. The RV enlargement demonstrated an independent association with mortality during hospitalization.

Key Words: Severe COVID-19 – RV abnormalities – In hospital outcome.

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Introduction

THE COVID-19 pandemic has led to millions infections around the world and thousands of mortalities. The attachment and entry of the virus occur by binding to angiotensin-converting enzyme 2 (ACE2). COVID-19 may cause multi-organ dysfunction, systemic inflammation, and severe illness. Additionally, the cardiovascular system can be involved **[1,2]**. Recent data have demonstrated that covid-19 infection presents with cardiovascular complications, as arrhythmias, heart failure, acute myocardial infarction, myocarditis, myocardial injury, and venous thrombo-embolism **[2-5]**. Most of these reports described its findings based on laboratory and clinical data (e.g troponin) without using cardiac imaging, may be because of the hazard of infection spread **[6]**. Hence, clinical assessment by different diagnostic modalities as electrocardiography, echocardiography, and cardiac magnetic resonance imaging, serum cardiac troponin, natriuretic peptide levels, and initial laboratory tests to assess for symptoms and signs of heart failure (HF) in addition to history and physical examination are essential. According to guidelines **[7]**, BNP/NT-proBNP biomarkers in COVID-19 patients should be assessed as the combination of the presence or extent of pre-existing cardiac disease and the acute hemodynamic stress related to COVID-19. Echocardiography, specifically cardiac imaging, is a fundamental tool for diagnosing numerous cardiac diseases and plays a pivotal role in assessing risk and guiding treatment decisions **[8]**. Acute SARS-CoV-2 infection has been related with increased risk of disseminated intravascular coagulation (DIC) and thromboembolic events such as superficial vein thrombosis or so-called venous thromboembolism (VTE) and pulmonary embolism **[9]**, albeit there were no other risk factors for thrombosis in these patients **[10]**. Also, recovered COVID-19 patients had a higher risk of PE and DVT compared with non-infected patients from the

general population [11]. Autopsies of covid-19 infected individuals showed small vessel pulmonary thrombosis and right ventricular dilatation [12]. As well, a recent report showed that covid-19 is accompanied by significant right ventricular dilation and systolic dysfunction [13].

Establishing the correlation between right ventricular dysfunction and in-hospital outcome would help in improving the medical care in patients with covid-19.

Aim of the work:

The main objective is to evaluate the prevalence of RV enlargement in patients with acute Covid-19. Additionally, we aim to evaluate the frequency of RV systolic function among patients with severe Covid-19 infection and investigate the association of RV dilatation and systolic dysfunction with the outcomes during hospitalization.

Patients and Methods

Setting:

In this study, 98 adult patients with acute severe COVID-19 infection who were admitted consecutively to ELMOKATTAM Health Insurance Hospital between August 2020 and February 2021, were included. Eight individuals were omitted (2 patients had poor echogenic window, 2 patients refused to participate in the study and 4 patients had past history of cardiovascular disease). All enrolled individuals had a confirmed COVID-19 infection by a positive reverse-transcriptase polymerase chain reaction assay in a respiratory tract sample. For the inclusion of acute COVID-19 patients in this study, diagnostic criteria were based on the guidelines outlined in the sixth edition of the Chinese National Health Commission on the diagnosis and treatment of COVID-19, issued on 18 February 2020 [14].

Study design:

Our study followed a cross-sectional prospective design.

Study population:

The study was conducted on 90 adult individuals (age d ≥18 years) admitted with acute severe covid-19 infection.

Inclusion criteria:

This study focused on adult individuals (aged 18 years and above) who were hospitalized due to acute severe COVID-19 infection, as classified by the existence of one or more of these criteria: oxygen saturation at or below 93%; respiratory rate >30/min; PaO2/FiO2 ratio ≤300; requirement of mechanical ventilation due to respiratory failure; shock; or respiratory failure accompanied by multiorgan dysfunction necessitating admission to ICU [15].

Exclusion criteria:

1- Patients refusing to participate in the study.
2- Patients in prone position.
3- Patients with previous known cardiovascular disease.
4- Patients with poor echogenic window.

Ethical considerations:

This study was conducted after obtaining approval from the Faculty of Medicine's Ethical committee, Cairo University.

Before inclusion in the study, all participants or their authorized representatives, if the participant was unable to provide consent, were required to provide informed written consent. The study's objectives and procedures were carefully clarified.

Study procedure:

Patients included in this study were subjected to the following:

Detailed history: Full history taking which comprised the age, name, gender, occupational status, profession, marital status. Important medical customs, past history of other medical diseases & current medications.

Physical examination: General examination including: Assessment of general appearance, body mass index (BMI). Essential indicators such as blood pressure measurement, assessment of the pulse, respiratory rate and temperature.

Laboratory findings were systematically recorded (including CBC, INR, renal function, liver function, troponin I, CK, CKMB, D dimer, CRP, ferritin and ABG. A CT score was determined for the chest imaging, with a threshold of 7 set to identify severe cases of COVID-19 based on the CT findings [16]. The lungs were partitioned into five lobes, and an individual assessment was conducted for each lobe. The disease-related abnormalities considered to be of significance encompassed the following manifestations: Ground-glass opacity, reticulation, nodule, consolidation, thickening of interlobular septa, linear opacities, crazy-paving pattern, curvilinear lines near the pleural surface, thickening of bronchial walls, enlargement of lymph nodes, and pleural and peri-cardial effusions. Based on the degree of lobe engagement, a CT score ranging from 0 to 5 was assigned to each lobe: score 0: no engagement; score 1: <5% engagement; score 2: 5-25% engagement; score 3: 26-49% engagement; score 4: 50-75% engagement; score 5: >75% engagement. The cumulative CT score, which encompassed the points allotted to each lobe, determined the overall score ranging from 0 to 25 points. With a sensitivity of 80.0% and specificity of 82.8%, the CT score cutoff of 7 was established to identify severe cases of COVID-19 [16]. A comprehensive transthoracic echocardiography using the same machine (GE vivid S6) by cardiologists specialized in conduct-

ing and analyzing echocardiography. Patients demonstrating symptom deterioration or worsening hemodynamics underwent a subsequent echocardiographic evaluation.

Examination method:

Cardiologists proficient in echocardiographic recording and interpretation utilized the GE Vivid S6 machine to perform echocardiography in a conventional manner. This procedure aimed to evaluate the following aspects:

1- From 4-chamber modified apical view including the entire right ventricle (RV), the evaluation of RV function involved the measurement TAPSE, systolic tricuspid lateral annular velocity (RV S') using TDI, and the assessment of RV dimension through the measurement of RV basal diameter in the apical 4-chamber view **[8]**. RV systolic dysfunction is defined as TAPSE less than 17 mm or S' velocity <9.5cm/sec by TDI. The criterion for defining RV dilatation is when the RV basal diameter exceeds 41mm **[8].**

2- Chamber dimensions and function, pulmonary hypertension, and valvular diseases through a customized level 1 focused protocol (BSE level 1 protocol) **[17].**

To adhere to the existing guidelines **[18]** and mitigate the risk of infection, specific precautions were implemented. All echocardiographic studies were conducted at the specified COVID-19 ICU as bedside examinations. To mitigate the potential spread of infection, the echocardiographic scanners were specifically allocated to the ICU specified for COVID-19 cases. During the echocardiographic recordings, adequate personal protection was ensured by implementing airborne precautions. This included the utilization of N-95 respirator masks, head covers, 2 sets of gloves, fluid-resistant gowns, eye shields, and shoe covers. To minimize exposure and contamination, electrocardiographic monitoring was excluded during the imaging procedure, and measurements were carried out offline.

Ultrasound device:

GE vivid S6 with 3S-RS Phased Array Transducer 3.5 GHz was employed for this study.

Statistical methods:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, interquartile range in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Multivariate regression analysis was done to assess independent predictors of in-hospital mortality. *p*-values less than 0.05 were considered as statistically significant.

Results

The baseline demographic characteristics and risk factors of the studied populations were as follow; mean age was 63.13±9.68 years, and 65 (72.2%) patients were males. Hypertension and diabetes mellitus were the most common comorbidities followed by smoking, chest disease and chronic kidney disease (as shown in Table 1).

Clinical characteristics of the studied populations were as follow; Nineteen (21.1%%) patients were intubated and mechanically ventilated at the time of the echocardiographic examination. The median time between admission and echocardiography was 2 days. Most patients had severe type 1 respiratory failure (partial pressure of oxygen <60mm Hg) with 12.2% requiring vasopressor support. 17 patients (18.9%) had died, of whom 9 (33.3%) had a RV abnormality (9 dilated, 4 impaired). Therapeutic anticoagulation was used in most of the cases (78.9%) (as shown in Table 2,3).

Regarding laboratory characteristics, most patients demonstrated elevated liver of D-dimer, ferritin and CRP [median (IQR): 1.21 (0.91-1.56), 467.5 (365-687) and 66 (48-94) respectively)] (as shown in Table 4).

Out of 90 patients, right ventricular dilatation was found in 25 patients (27.8%) and right ventricular systolic dysfunction was found in 10 patients (11.1%) with right ventricular abnormality (dilatation and/or dysfunction) found in 27 patients (30%) with 2 patients only had right ventricular systolic dysfunction with dilatation (as shown in Tables 5,6).

Regarding the prevalence of RV dilatation or systolic dysfunction and CT chest severity; out of 90 patients, CT chest was severe in 24 (28.6%) patients with RV dilatation and 9 (10.7%) patients with RV systolic dysfunction (as shown in Table 7).

RV abnormality was associated with more in-hospital mortality ($p<0.001$), mechanical ventilation ($p<0.001$), CKD ($p=0.028$) and shock ($p=0.003$) (as shown in Table 8).

Relation of RV abnormality (RV dilatation and systolic dysfunction) and echocardiography parameters:

RV abnormality was associated with higher incidence of LV diastolic dysfunction, tricuspid regurgitation, pulmonary regurgitation and pulmonary hypertension (*p*: 0.015, <0.001, <0.001 and <0.001 respectively) (as shown in Table 9).

Relation of RV abnormality (RV dilatation and systolic dysfunction) and laboratory findings: RV abnormality was associated with decreased po2 (partial pressure of oxygen) (*p*: 0.036). Also, RV abnormality was associated with increased TLC (total leucocytic count), CK (creatinine kinase), CKMB (creatinine kinase myocardial band), creatinine, D-Dimer, ferritin and CT chest severity score (*p*:0.048, *p*:0.006, *p*:0.016, *p*:0.016, *p*:0.015, *p*:0.036, *p*:0.004, *p*: 0.004, *p*:<0.001, *p*:0.006 respectively). Also, RV abnormality was associated with positive troponin (*p*:<0.001).

Relation of RV dilatation & dysfunction with in-hospital mortality:

RV dilatation & RV dysfunction was associated with increased in-hospital mortality (*p*<0.001 and 0.012 respectively) (as shown in Tables 13,14).

Table (1): Baseline demographic characteristics and risk factors.

	Mean ± SD/ Count (percentage)
Age	63.13±9.68
Gender	Male 65 (72.2%)
BMI	27.4±2.6
DM	53 (58.9%)
HTN	53 (58.9%)
Smoking	25 (27.8%)
Previous stroke	1 (1.1%)
Chest disease	10 (11.1%)
CKD	10 (11.1%)

BMI : Body mass index. HTN : Hypertension.
DM : Diabetes mellitus. CKD : Chronic kidney disease.

Table (2): Clinical characteristics.

	Median (IQR) / Count (percentage)
SBP	130 (110-140)
DBP	80.00 (70-90)
Respiratory rate	32.00 (29-34)
O2 Saturation	80.00 (76-84)
heart rate	97.00 (91-105)
days on MV	3.00 (2-3)
Invasive mechanical ventilation	23 (25.6%)
Shock	12 (13.3%)
In-hospital mortality	18 (20%)
In-hospital stay	16 (14-19)
Atrial tachyarrhythmia	10 (11.1%)
Ventricular tachyarrhythmia	1 (1.1%)
Prolonged QT	1 (1.1%)
CT chest severity score	14.5 (11-18)
Severe CT chest	84 (93.3%)
Time from admission to echo	2 (1-2)
Therapeutic anticoagulation	71 (78.9%)
Corticosteroid	90 (100%)
vasopressors	12 (13.3%)
Fluid infusion	12 (13.3%)
Azithromycin / hydro chloroquine	89 (98.9%)

SBP : Systolic blood pressure.
DBP : Diastolic blood pressure.
MV : Mechanical ventilation.

Table (3): Echocardiographic characteristics.

		Mean± SD/ Median (IQR) / Count (percent)
Left atrial diameter (cm)		3.7 (3.4-4.0)
Left ventricle end-diastolic diameter (cm)		5.25 (4.7-5.6)
Left ventricle end-systolic diameter (cm)		3.4 (2.8-3.9)
Left ventricle ejection fraction (%)		64 (57-70)
Wall motion score index (WMSI)		1.127±0.347
Aortic root diameter (cm)		3.1 (2.8-3.4)
Right ventricular basal diameter (cm)		3.7 (3.4-4.3)
TAPSE (mm)		2 (1.8-2.2)
S' velocity using TDI (cm/s)		17 (14-19)
ePASP (mmHg)		38 (27-51)
Left ventricular diastolic dysfunction	Grade I	44 (48.9%)
	Grade II	24 (26.7%)
	Grade III	7 (7.8%)
Aortic regurgitation	Mild	3 (3.3%)
	Moderate	4 (4.4%)
	Severe	1 (1.1%)
Aortic stenosis	Mild	3 (3.3%)
Mitral regurgitation	Mild	22 (24.4%)
	Moderate	2 (2.2%)
	Severe	3 (3.3%)
Tricuspid regurgitation	Mild	21 (23.3%)
	Moderate	7 (7.8%)
	Severe	6 (6.7%)
Pulmonary regurgitation	Mild	20 (22.2%)
Pulmonary hypertension		23 (25.6%)
Pericardial effusion	Mild	15 (16.7%)
	Moderate	1 (1.1%)

TAPSE : Tricuspid annular plane systolic excursion.
TDI : Tissue Doppler imaging.
ePASP : Estimated pulmonary artery systolic pressure.

Table (4): Laboratory characteristics.

	Median (IQR)/ count (%)
TLC (Thousands /cubic millimeter)	8.4 (5.9-10.5)
Lymphocytes count (Thousands /cubic millimeter)	1 (0.8-1.2)
Hb (g/dl)	12.65 (11.3-14)
PLT (× 10^ 9 /L)	223 (176-270)
INR	1.1 (1.02-1.2)
CK (U/L)	85 (58-156)
CK-MB (U/ml)	21 (16-35)
Urea (mg/dl)	51 (43-71)
Creatinine (mg/dl)	1.1 (0.86-1.34)
ALT (U/L)	34 (24-40)
AST (U/L)	33.5 (26-41)
PH	7.39 (7.36-7.43)
PaCO2 (mmHg)	32 (30-35)
PaO2 (mmHg)	51 (47-53)
HCO3 (mmol/L)	21 (20-23)
CRP (mg/L)	66 (48-94)
Ferritin (mcg/L)	467.5 (365-687)
D-DIMER	1.21 (0.91-1.56)
Troponin I (positive)	9 (10%)

TLC : Total Leucocyte Count.
Hb : Hemoglobin.
PLT : Platelet count.
INR : International Normalized Ratio.
CK : Creatine Kinase.
ALT : Alanine Aminotransferase.
AST : Aspartate Transferase.
PaO2 : Partial pressure of oxygen.
PaCO2 : Partial pressure of carbon dioxide.
Bicarbonate : HCO3.
CRP : C-reactive protein.

Table (5): Percentages of cases with and without RV (right ventricle) dilatation and systolic dysfunction.

	Count (%)
Right ventricular dilatation	25 (27.8%)
Right ventricular systolic dysfunction	10 (11.1%)

Table (6): Percentages of cases with and without RV abnormalities (dilatation and systolic dysfunction).

	Count (percent)
Right ventricular abnormality	27 (30.0%)

Table (7): Percentages of cases with RV dilatation and systolic dysfunction and CT chest severity.

	CT chest severity score	
	Severe	Not Severe
	Count (%)	Count (%)
Right ventricular dilatation	24 (28.6%)	1 (16.7%)
Right ventricular systolic dysfunction	9 (10.7%)	1 (16.7%)

Table (8): Relation of RV abnormality (RV dilatation and systolic dysfunction) and other parameters.

	Right ventricular abnormality		*p*-value
	Abnormal	Normal	
	Mean ± SD/ Count (%)	Mean ± SD/ Count (%)	
Age	65 (9.6)	62.3 (9.7)	0.225
Gender	20 (74.1%)	45 (71.4%)	0.797
BMI	28 (3)	27 (3)	0.373
DM	18 (66.7%)	35 (55.6%)	0.326
HTN	17 (63.0%)	36 (57.1%)	0.607
Smoking	4 (14.8%)	21 (33.3%)	0.072
Previous stroke	0 (0.0%)	1 (1.6%)	1
Chest disease	5 (7.9%)	5 (14.8%)	0.143
CKD	6 (22.2%)	4 (6.3%)	0.028
Shock	8 (29.6%)	4 (6.3%)	0.003
Atrial tachyarrhythmia	6 (22.2%)	4 (6.3%)	0.060
Ventricular tachyarrhythmia	0 (0.0%)	1 (1.6%)	1
Prolonged QT	1 (3.7%)	0 (0.0%)	0.300
Invasive mechanical ventilation	14 (51.9%)	9 (14.3%)	<0.001
In-hospital mortality	14 (44.4%)	6 (9.5%)	<0.001

BMI : Body mass index. HTN : Hypertension.
DM : Diabetes mellitus. CKD : Chronic kidney disease.

Table (9): Relation of RV abnormality (RV dilatation and systolic dysfunction) and echocardiography parameters.

	RV abnormality		*p*-value
	Abnormal	Normal	
	Count (%)	Count (%)	
Left ventricular diastolic dysfunction grade:			
Grade I	13 (48.1%)	31 (49.2%)	0.015
Grade II	10 (37.0%)	14 (22.2%)	
Grade III	4 (14.8%)	3 (4.8%)	
Pericardial effusion:			
Mild	7 (25.9%)	8 (12.7%)	0.083
Moderate	1 (3.7%)	0 (0.0%)	
Aortic regurgitation:			
Mild	1 (3.7%)	2 (3.2%)	0.746
Moderate	2 (7.4%)	2 (3.2%)	
Severe	0 (0.0%)	1 (1.6%)	
Aortic stenosis:			
Mild	0 (0.0%)	3 (4.8%)	0.249
Mitral regurgitation:			
Mild	5 (18.5%)	17 (27.0%)	0.414
Moderate	1 (3.7%)	1 (1.6%)	
Severe	2 (7.4%)	1 (1.6%)	
Mitral stenosis:			
None	27 (100.0%)	63 (100.0%)	–
Tricuspid regurgitation:			
Mild	10 (37%)	12 (19%)	<0.001
Moderate	4 (14.8%)	3 (4.8%)	
Severe	5 (18.5%)	1 (1.6%)	
Pulmonary regurgitation:			
Mild	16 (59.3%)	4 (6.3%)	<0.001
Pulmonary hypertension	17 (63%)	6 (9.5%)	<0.001

Table (10): Relation of RV abnormality (RV dilatation and systolic dysfunction) and management.

	RV abnormality		*p*-value
	Abnormal	Normal	
	Count (%)	Count (%)	
Therapeutic anticoagulation	23 (85.2%)	48 (76.2%)	0.338
Azithromycin & Hydroxychloroquine	26 (96.3%)	63 (100.0%)	0.300
Corticosteroid	27 (100.0%)	63 (100.0%)	–
Vasopressors	8 (29.6%)	4 (6.3%)	0.003
Saline infusion	5 (18.5%)	7 (11.1%)	0.335

Table (11): Relation of RV abnormality (RV dilatation and systolic dysfunction) and vital signs.

	RV abnormality		*p*-value
	Abnormal	Normal	
	Median (IQR)	Median (IQR)	
Age (years)	65.00 (62-72)	65.00 (55-70)	0.926
BMI	27 (26-30)	27 (26-29)	0.963
SBP (mmHg)	110.00 (100-140)	130.00 (120-140)	0.597
DBP (mmHg)	70.00 (60-80)	80.00 (70-90)	0.422
Respiratory rate (cycle/min)	33.00 (29-36)	32.00 (29-34)	0.328
Oxygen Saturation (%)	76.00 (72-80)	81.00 (79-85)	<0.001
Heart rate (beat /min)	103.00 (92-112)	96.00 (91-101)	0.072
Days on MV	2.00 (2-3)	3.00 (3-4)	0.343
In-hospital stay (days)	14 (3-23)	16 (15-19)	0.926

BMI : Body mass index. DBP : Diastolic blood pressure.
SBP : Systolic blood pressure. MV : Mechanical ventilation.

Table (12): Relation of RV abnormality (RV dilatation and systolic dysfunction) and laboratory findings.

	RV abnormality		*p*-value
	Abnormal	Normal	
	Median (IQR) / count (%)	Median (IQR) / count (%)	
TLC (Thousands /cubic millimeter)	9.60 (6.2-14)	8.30 (5.6-10)	0.048
Lymphocytes count (Thousands /cubic millimeter)	1.00 (0.7-1.2)	1.00 (0.8-1.2)	0.712
Hb (g/dl)	11.90 (10.5-13.6)	12.80 (11.5-14.2)	0.645
PLT (× 10^ 9 /L)	230.00 (168-356)	217.00 (176-261)	0.890
INR	1.10 (1.03-1.29)	1.09 (1.02-1.2)	0.121
CK (U/L)	113.00 (79-284)	79.00 (65-107)	0.006
CK-MB (U/ml)	25.00 (19-56)	19.00 (13-27)	0.016
Urea (mg/dl)	62 (40-87)	51 (43-64)	0.293
Creatinine (mg/dl)	1.23 (0.93-1.67)	1 (0.83-1.2)	0.015
ALT (U/L)	38 (24-48)	34 (24-39)	0.381
AST (U/L)	38 (26-43)	32 (25-41)	0.358
PH	7.40 (7.34-7.43)	7.39 (7.36-7.43)	0.579
PaCO2 (mmHg)	32 (29-35)	32 (30-36)	0.963
PaO2 (mmHg)	48 (43-51)	51 (49-53)	0.036
HCO3 (mmol/L)	21 (18-24)	21 (2)	0.854
CRP (mg/L)	88 (42-106)	60 (48-82)	0.097
D-DIMER	1.64 (0.93-2.3)	1.1 (0.9-1.35)	0.004
Ferritin (mcg/L)	723 (673-857)	412 (299-489)	<0.001
CT chest severity score	16 (14-19)	13 (10-17)	0.006
Time from admission to echo (days)	2 (1-2)	2 (1-2)	0.782
Troponin I (positive)	8 (29.6%)	1 (1.6%)	<0.001

TLC : Total Leucocyte Count. INR : International Normalized Ratio. PaO2 : Partial pressure of oxygen.
Hb : Hemoglobin. CK : Creatine Kinase. PaCO2 : Partial pressure of carbon dioxide.
PLT : Platelet count. ALT : Alanine Aminotransferase. Bicarbonate : HCO3.
AST : Aspartate Transferase. CRP : C-reactive protein.

Table (13): Relation of RV dilatation and in-hospital mortality.

	RV dilatation		*p*-value
	Abnormal	Normal	
	Count (%)	Count (%)	
In-hospital mortality:			
Yes	12 (48.0%)	6 (9.2%)	<0.001

Table (14): Relation of RV systolic dysfunction and in-hospital mortality.

	RV systolic dysfunction		*p*-value
	Abnormal	Normal	
	Count (%)	Count (%)	
In-hospital mortality:			
Yes	5 (50.0%)	13 (16.3%)	0.012

Table (15): Logistic regression analysis to evaluate independent predictors of mortality during hospitalization.

	OR	CI	*p*-value
Right ventricular dilatation	6.130	1.368 - 27.469	0.018
Total leucocytic count	1.238	1.013 - 1.512	0.037
Oxygen saturation	0.778	0.678 - 0.894	<0.001

Regression analysis to assess independent predictors of in-hospital mortality:

Independent predictors of in-hospital mortality were assessed using a regression analysis that includes RV dilatation, RV systolic dysfunction, pulmonary hypertension, left ventricle ejection fraction, troponin, shock, O2 saturation, WBCs count, CRP and D-dimer. Forward stepwise selection was used to derive the final model for which significance levels of 0.1 and 0.05 were chosen to exclude and include terms, respectively. Multivariate analysis showed that WBC count, O2 saturation and RV dilatation were independent predictor of in-hospital mortality.

Discussion

Implication and significance of right ventricular abnormalities in severe COVID 19 patients.

Despite that recent studies demonstrated that COVID 19 is associated with significant right ventricular dilatation and systolic dysfunction **[13,19]**, most of those were performed on COVID 19 patients without adhering to a certain severity criterion. Moreover, since the beginning of the pandemic, research has stated that mortality rate among COVID 19 patients was highest among severe cases **[20]**.

Therefore, it is reasonable to assume that by recognizing the prevalence of RV abnormalities in severe COVID 19 patients, this would aid the physicians in customizing the treatment approaches for individuals diagnosed with COVID-19, and identifying the underlying pathogenesis. In addition, recognizing right ventricular abnormalities relation to in-hospital outcome may be used as a prognostic tool by identifying which patients may be at highest risk. Therefore, in our prospective study, we aimed to evaluate the prevalence of RV dilatation and systolic dysfunction by echocardiography in 90 consecutive individuals with acute COVID 19 infection and follow-up of those patients to correlate RV abnormalities with in-hospital outcome.

Prevalence of right ventricular dysfunction in COVID 19:

The mechanism of RV dysfunction in COVID 19 presumed to involve multiple factors and can demonstrate variability throughout various stages of the disease. In cases of severe adult respiratory distress syndrome (ARDS) or pulmonary embolism **[21]**, isolated RV dysfunction can be observed. Additionally, the overall impairment of RV function may be attributed to viral toxicity and the immune response of the host, leading to diffuse myocardial damage. The presence of ACE2 expression in the endothelium makes it susceptible to virus-induced endothelial shedding and microvascular injury, which can potentially result in thrombosis and myocardial infarction **[21]**. During the initial stages of COVID-19, ACE2-mediated direct injury is believed to be a significant mechanism. As the disease progresses, pulmonary and cardiac damage intensifies due to worsening hypoxia. Inflammatory responses and autoimmune-related harm contribute significantly to the deterioration observed in the later stages of COVID-19.

In our study, RV abnormalities were found in 27 patients out of 90 (30%) with RV dilatation as the most common (25 patients, 27.8%) followed by RV systolic dysfunction (10 patients, 11.1%).

Consistent with a previous study **[13]** conducted on a cohort of 74 patients, which aimed to define the echocardiographic characteristics of individuals with COVID-19 pneumonia and their correlation with biomarkers, it was found that RV dilatation and dysfunction are frequently observed in COVID-19 pneumonia patients, along with increased HS Tn-I levels. Most of the patients exhibited acute type 1 respiratory failure (partial pressure of oxygen <8 kPa or <60mm Hg. The RV dilatation was observed in 41%, while 27% showed impaired RV function. Conversely, impairment of the left ventricle is infrequent, with a more frequent occurrence of hyperdynamic function. Also, a previous study **[19]** evaluated a cohort of 100 COVID-19 patients to determine the prevalence of cardiac abnormalities through echocardiography. The findings revealed

that the most prevalent abnormality was RV dilation, with or without associated dysfunction, while systolic LV dysfunction was notably infrequent.

Patients in our study with RV abnormalities had more severe lung disease based on CT chest severity score (median, IQR: 16 (14-19), p=0.006). Also, RV abnormalities was associated with less oxygen saturation (p<0.001), shock (p=0.003), more use of ventilation (p<0.001) and vasopressors (p: 0.003). This reinforces the idea that RV dysfunction is multifactorial and is contributed to cytokine release, hypoxemic vasoconstriction, thrombotic events, and direct viral damage [19,22,23].

Relation of Right ventricular abnormalities, cardiac and inflammatory biomarkers:

Initial reports from China indicated that a significant proportion of COVID-19 patients exhibited elevated levels of cardiac biomarkers [24,25]. In particular, there was a demonstrated correlation between elevated levels of troponin and brain natriuretic peptide with increased D-dimer levels, which served as predictors of unfavorable outcomes [26]. Furthermore, significant associations were observed between inflammatory markers, including procalcitonin (PCT), interleukin-6 (IL-6), serum ferritin, and C-reactive protein (CRP), and an increased risk of developing severe COVID-19 [27,28].

Patients with RV abnormalities in our study showed higher levels of D-dimer (p=0.004), ferritin (p<0.001), Troponin (p: <0.001), CKMB (p= 0.016), creatinine (p=0.015) and TLC (p=0.048).

Our study was partially in agreement with another study [13] mentioned previously. The study demonstrated that RV systolic dysfunction was significantly linked to increased D-dimer (p=0.003) and CRP (p=0.045) but was not linked to HS Tn-I.

Our data are in contrast with another study [29] which aimed to assess the right ventricular size and its association with in-hospital mortality in 105 COVID 19 patients. The study demonstrated that patients with RV dilatation did not exhibit substantial variances in the laboratory markers of inflammation (white blood cell count) or myocardial injury (troponin I). However, the study was in concert with our study that patients with RV dilatation had a higher likelihood of experiencing renal dysfunction (p=0.001), and that there was no significance difference in C-reactive protein.

It should be underlined that the discrepancy might arise from methodological issues (such as selection of severe COVID-19 patients in our study).

Relation of Right ventricular abnormalities and other echocardiographic parameters:

Patients with RV abnormalities in our study showed associated tricuspid regurgitation (p< 0.001), LV diastolic dysfunction (p<0.015) and pulmonary hypertension (p<0.001). Moreover, pulmonary hypertension & pulmonary regurgitation were a common finding in our study population (25.5% and 22.2% respectively). Although RV abnormality was associated with LV diastolic dysfunction, it should be noted that in our study grade I diastolic dysfunction was very common (13 (48.1%) of all patients with RV abnormality) and most of the patients in our study had old age (median-IQR: 65 -15) in which whom grade I diastolic dysfunction as a normal process of age [30]. No relation of RV abnormalities with other echocardiographic parameters were statistically significant.

These findings were consistent with another study [31] performed on 200 hospitalized, non-ICU COVID-19 patients to examine the characteristics, prevalence, and prognostic significance of pulmonary hypertension (PH) and RV dysfunction. This study demonstrated that PH patients exhibited significantly larger basal RV end-diastolic diameter (42 (38–48) vs 36 (32–39) mm, p<0.001) and mid RV end-diastolic diameter (37 (31–40) vs 30 (26–32) mm, p<0.001), and lower TAPSE (20 (17–22) vs 22 (20–25) mm, p=0.004) and S' wave (12 (9–13) vs 13 (11–15) cm/s, p=0.004) compared with patients without PH.

These observations can be attributed to secondary changes in pulmonary vascular hemodynamics occurring during ARDS due to factors such as hypoxia, elevated alveolar pressure, vascular remodeling or compression by edema or fibrosis, localized thrombosis or pulmonary embolism, vasoconstriction, and decreased pulmonary compliance resulting from the use of EEP) [32,33].

Of note, most patients exhibited normal left ventricular systolic function (EF median (IQR): 64 (13.3) and only 10% of the patients had EF less than 50%.

Relation of Right ventricular abnormalities with in-hospital outcome:

In our study, right ventricular abnormalities revealed association with higher mortality during hospitalization (p=0.022). RV dilatation revealed association with higher mortality during hospitalization (p<0.001). Also, RV systolic dysfunction revealed association with higher mortality during hospitalization (p=0.012).

Using multivariate logistic regression analysis, RV dilatation revealed independent association with higher mortality during hospitalization (odds ratio: 6.13, confidence interval: 1.368-27.469, p:0.018) along with WBC count and O2 saturation).

Our data regarding RV dilatation correlated with the results of another study [29] on 105 patients where multivariate analysis demonstrated that RV enlargement was the sole variable signifi-

cantly linked to mortality (odds ratio: 5.422; 95% confidence interval: 1.418 to 20.741; p=0.014).

The correlation of RV abnormalities and poor prognosis could be explained by the fact that COVID-19 is often correlated with chest CT scans findings of bilateral multi-lobar ground-glass opacities ***[34]***, and associated hypoxic respiratory failure, which can increase RV afterload. Additionally, COVID-19 has the potential to increase the likelihood of venous thrombotic events, including pulmonary embolism, which can be contribute to an elevated RV afterload ***[35]***. RV dysfunction, in turn, diminishes cardiac output. Additionally, the displacement of the interventricular septum towards the left can impact LV diastolic filling and decrease systemic output ***[36]***.

Follow-up echocardiography to clinically deteriorating patients:

A second echocardiography was done on 9 patients (10%) who exhibited deterioration of symptoms or worsening of hemodynamics. Five of the 9 patients revealed changes in the echocardiography parameters (3 patients revealing further dilatation of right ventricle, 1 patient revealed declining in RV systolic function while 1 patient showed decrease in LV systolic function), while 4 patients didn't demonstrate significant changes in the follow up echocardiography.

Conclusion:

In the present study, focused and time-efficient echocardiography was utilized to assess hospitalized patients with severe COVID-19 infection, revealing a high prevalence of RV dilation. RV systolic dysfunction was the second most common finding and RV dilatation revealed independent association with mortality during hospitalization.

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اعتلالات البطين الأيمن فى المرضى المحجوزين بالمستشفى ويعانون من التهاب شديد كوفيد ١٩

تضمنت هذه الرساله ٩٠ مريضاً يعانون من التهاب شديد بكوفيد ١٩ محجوزين بمستشفى المقطم للتأمين الصحى فى الفتره من أغسطس ٢٠٢٠ إلى فبراير ٢٠٢١.

تم التأكد من تشخيص كافه المرضى فى الدراسه بفيروس كوفيد ١٩ عن طريق ايجابيه اختبار تفاعل البوليميراز المتسلسل.

معايير الاستبعاد تضمنت رفض المريض المشاركه فى الدراسه أو مريض فى وضعيه الانبطاح أو المرضى الذين يعانون من أمراض قلب سابقه.

تم الحصول علي البيانات الإكلينيكيةّ من جميع المرضى، وتم تسجيل النتائج المعمليه بشكل منهجى مع موجات صوتية على القلب عبر الصدر.

كانت نقطة النهاية الأولية للبحث هي حدوث تمدد بالبطين الأيمن في مرضى كوفيد ١٩ الشديد، والنقاط النهائية الثانوية هي حدوث اختلال بالوظيفة الانقباضية للبطين الأيمن وربط نسبة التمدد او الأختلال بوظيفة البطين الأيمن بتطور الحالة الصحية للمريض داخل المستشفى.

أهم الاستنتاجات والنتائج التطبيقيه التى تم التوصل اليها:

١- اعتلالات البطين الأيمن شائعه فى المرضى الذين يعانون من عدوى كوفيد ١٩ شديده

٢- ارتبط تمدد البطين الأيمن بشكل مستقل بالوفيات داخل المستشفى فى الدراسة الحالية

٣- الكشف المبكر لاعتلالات البطين الأيمن يؤدى إلى علاج دقيق والمساعده فى الحد من الوفيات.

٤- يجب متابعه أبعاد و وظيفه البطين الأيمن الانقباضيه فى المرضى الذين يعانون من عدوى كوفيد ١٩ شديده لتحسين متغيرات العلامات الحيويه والتنفسيه.