



Right Ventricular Assessment in Critically Ill COVID-19 Patients and its Prognostic Importance

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Abstract

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BACKGROUND: Cardiac injury is a prevalent complication and is associated with worse prognosis in COVID-19 patients. The increased cardiac workload resulting from respiratory failure and hypoxemia is a common mechanism of cardiac injury, and the right ventricle may bear the brunt of its impact.

AIM: The present study aimed to determine the incidence and prognostic value of right ventricular (RV) dysfunction in COVID-19 patients admitted to the intensive care unit using conventional echocardiography parameters.

METHODS: Patients were subjected to full history taking and clinical examination, computed tomography (CT) of the chest was done for all patients to assess the severity of lung infiltration, all patients received standard treatment according to Ministry of Health and Population COVID-19 treatment protocol recommendations. The echocardiographic assessment was done on all patients.

RESULTS: The mean age of the patients was 61.10 ± 9.64 years (range 42–80 years). There were 36 (60%) males and 24 (40%) females. The nonsurvivor group consisted of 28 patients (46.7%), and the survivors consisted of 32 patients (53.3%). There was a statistically significant association between mortality and RV function regarding tricuspid plane systolic excursion, fractional area change %, RV basal diameter, and expiratory positive airway pressure.

CONCLUSION: We concluded that in COVID-19 patients, RV function must be assessed and its prognostic importance recognized. RV dysfunction is not only a symptom of high pulmonary pressures, but it also contributes to cardiac insufficiency.

Introduction

The pandemic started Starting December 2019, when a novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Due to its high infectivity and potentiality of severe disease and complications, it was addressed as “Public Health Emergency of International Concern” by the World Health Organization on January 30, 2020 [2]. On the cellular level, in the lungs, where the virus receptor, the SARS-CoV-2 affects host cells by binding the spike protein (protein S) expressed in the viral envelope with the membrane-bound angiotensin-converting enzyme 2 (ACE2). This will result in endocytosis of the SARS-CoV-2 and ACE2 complex, resulting in the viral entry into the cell [3]. Binding of the SARS-CoV-2 with ACE2 will produce RAAS imbalance affecting the blood pressure, cardiovascular, renal, immune, and neural systems homeostasis [4], [5]. One of the worst prognosis indices in COVID-19 is cardiac injury which can be explained by the increased cardiac workload from respiratory failure and hypoxemia, mainly affecting the right ventricle. Echocardiography is a widely

available imaging tool for assessing cardiac function. Although both left ventricular (LV) dysfunction and right ventricular (RV) dysfunction are noted in hospitalized COVID-19 patients, the incidence of RV dysfunction is associated with more clinical deterioration (i. e., hemodynamic instability, cardiac deterioration, and respiratory deterioration) [6].

We aimed to determine the incidence and prognostic value of RV dysfunction in COVID-19 patients admitted to the intensive care unit (ICU) using conventional echocardiography parameters.

Methods

Study population

Our study included 60 patients (36 males and 24 females) above 18 years old, all patients were subjected to full history taking, and clinical examination, chest computed tomography. Broad-spectrum, antibiotics treatment was immediately initiated after

clinical evaluation within 1 h of presentation and received standard treatment according to Ministry of Health and Population COVID-19 treatment protocol recommendations.

Our inclusion criteria included:

- Positive COVID-19 nasopharyngeal swab PCR result
- ICU admission criteria: (RR>30, SaO₂<92% or PaO₂/FiO₂<200 despite oxygen therapy)
- Computed tomography CT chest showed more than 50% affection or progressive lesion within 24–48 h.

Our exclusion criteria included:

- Echocardiographic evidence of regional ischemia
- Previous infarction or significant valvular heart disease
- Echocardiographic evidence of ejection fraction of <50%
- Mechanical ventilation before the echocardiographic evaluation
- Any cause of pulmonary hypertension, e.g., Chronic obstructive pulmonary disease, interstitial lung disease, chronic thromboembolic disease, etc.
- Patients with poor echocardiographic windows.

Echocardiographic assessment

Assessment of the right side of the heart

Measurement of the tricuspid plane systolic excursion

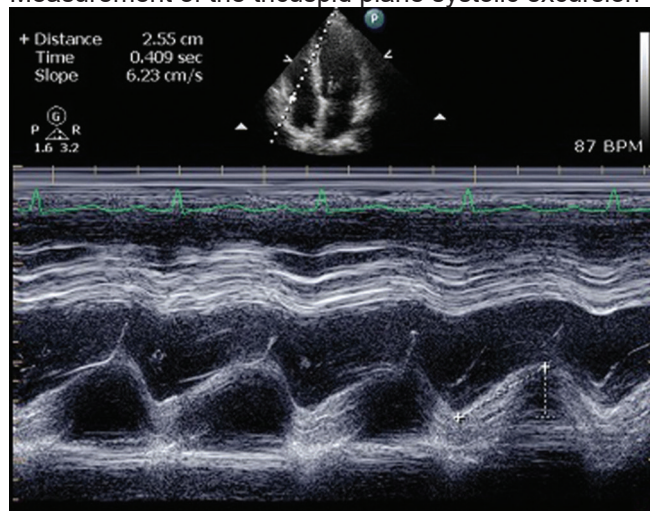


Figure 1: Measurement of the tricuspid plane systolic excursion

Tricuspid plane systolic excursion (TAPSE) was obtained by measuring the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical four-chamber window using m-mode echocardiography. Normal values of TAPSE: (1.6–3 cm).

Measurement of the right ventricular area and calculation of the fractional area change (Figure 2).

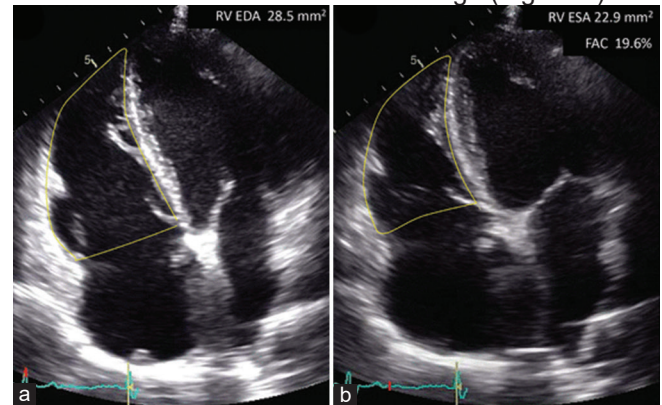


Figure 2: Measurement of the right ventricular area and calculation of the fractional area change

- Right ventricular area and calculation of the fractional area change (RVFAC) were obtained from a four-chamber view by tracing the RV endocardium both in systole and diastole from the annulus, along the free wall to the apex, and then back to the annulus, along the interventricular septum.
- $RVFAC = \frac{RV \text{ end-diastolic area} - RV \text{ end-systolic area}}{RV \text{ end-diastolic area}}$
- Normal values of RVFAC: 35%–63%.

Measurement of the right ventricular dimensions long (basal, mid, and long) (Figure 3).

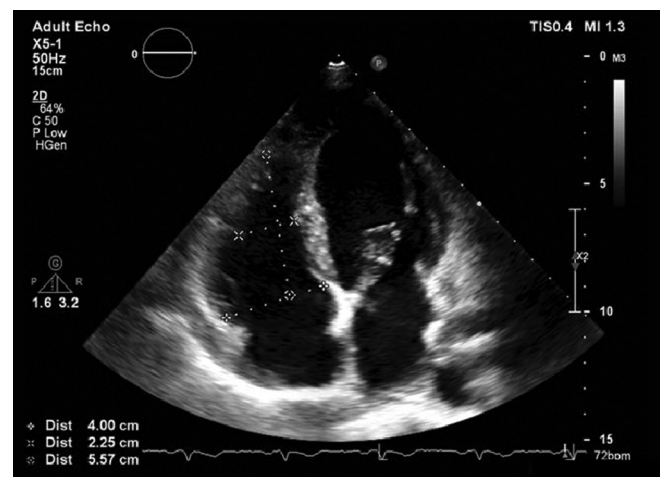


Figure 3: Measurement of the right ventricular dimensions (basal, mid, and long)

From the apical four-chamber view, the basal diameter was measured in the basal one-third of the right ventricle, the mid cavity diameter was measured in the middle-third of the right ventricle at the level of the LV papillary muscles, and the longitudinal diameter was drawn from the plane of the tricuspid annulus to the RV apex.

Normal values:

- (RV basal dimension: 2.4–4.2 cm)
- (RV mid dimension: 2–3.5 cm)
- (RV long dimension: 5.6–8.6 cm).

Systolic pulmonary artery pressure (Figure 4).

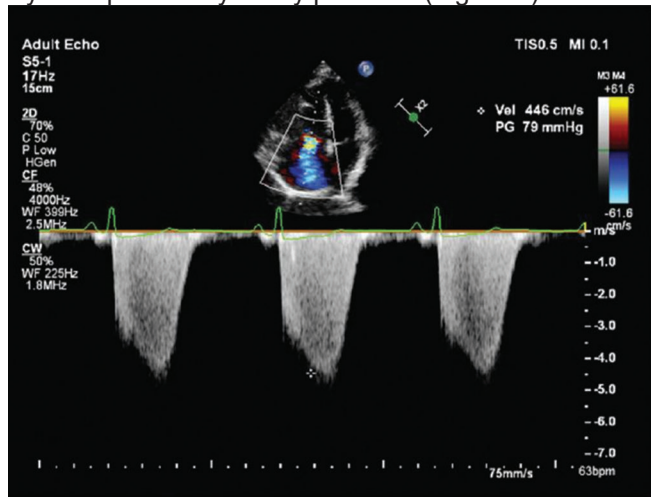


Figure 4: Systolic pulmonary artery pressure

Pulmonary artery systolic pressure was estimated by calculating the systolic pressure gradient between RV and RA by continuous-wave Doppler of the tricuspid regurgitation jet. RV systolic pressure (RVSP) was determined from peak TR jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure: $RVSP = 4(V)^2 + RA \text{ pressure}$, where V is the peak velocity (in meters per second) of the tricuspid valve regurgitant jet, and RA pressure was estimated from central venous catheter pressure.

Assessment of the left side of the heart

Left ventricular dimensions

- LV end-diastolic diameter
- LV end-systolic diameter
- Septal wall thickness
- Posterior wall thickness.

Left ventricular EF %

LV ejection fraction will be calculated from LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) estimates, using the following formula: $EF = (EDV - ESV) / EDV$. That was done using modified Simpson's rule which was based on tracings of the blood-tissue interface on the apical four and apical two-chamber views at the end of systole and diastole.

Mitral inflow pattern

- Peak E (early diastolic) wave velocity
- Peak A (atrial filling) wave velocity
- E/A ratio.

Statistical analysis

Recorded data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation.

Qualitative data were expressed as frequency and percentage. The following tests were done: Independent-sample t-test of significance was used when comparing between two means. Mann-Whitney U-test: For two-group comparisons in nonparametric data. Chi-square test of significance was used to compare proportions between qualitative parameters. $p < 0.05$ was considered statistically significant. $p < 0.001$ was considered highly significant. $p > 0.05$ was considered insignificant.

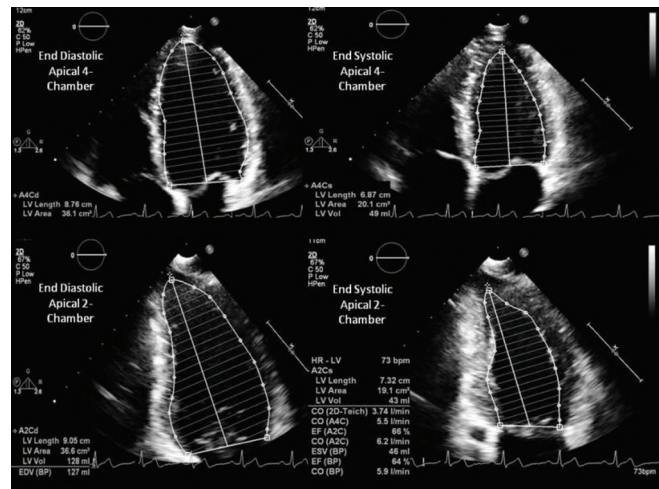


Figure 5: LV ejection fraction will be calculated from LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) estimates

Results

The mean age of the patients was 61.10 ± 9.64 years (range 42–80 years). There were 36 (60%) males and 24 (40%) females. The demographic data are shown in Table 1 and the echocardiographic data are shown in Table 2.

Table 1: Baseline demographic data

Demographic data	Total (n = 60)
Sex, n (%)	
Male	36 (60.0)
Female	24 (40.0)
Age (years)	
Range	42–80
Mean ± SD	61.10 ± 9.64

SD: Standard deviation.

Table 2: Echocardiography data

Echocardiography data	Mean ± SD
LV function	
EDD	4.94 ± 0.46
ESD	3.08 ± 0.48
EF %	64.58 ± 7.71
RV function	
TAPSE	2.01 ± 0.60
FAC %	35.42 ± 7.81
RV basal diameter	3.79 ± 0.95
EPAP	27.82 ± 8.04
Echocardiography data	Normal, n (%) Abnormal, n (%)
TAPSE (N>1.6 cm)	35 (58.3) 25 (41.6)
FAC % (N>35%)	34 (56.6) 26 (43.3)
RV basal diameter (N<4.2 cm)	37 (61.6) 23 (38.3)
EPAP (N<35 mmhg)	45 (75) 15 (25)
TR	n (%)
No	2 (3.3)
Mild	30 (50)
Moderate	24 (40)
Severe	4 (6.7)

SD: Standard deviation, LV: Left ventricular, EDD: End-diastolic diameter, ESD: End-systolic diameter, EF: Ejection fraction, RV: Right ventricular, TAPSE: Tricuspid plane systolic excursion, FAC: Fractional area change, EPAP: Estimated Pulmonary Artery Pressure, TR: Tricuspid Regurgitation.

The nonsurvivor group consisted of 28 patients (46.7%), and the survivors consisted of 32 patients (53.3%). There was a statistically significant association between mortality and increased TLC ($p = 0.008$), lower Hb ($p = 0.002$), and decreased PLTs ($p = 0.003$); there was a highly statistically significant association between mortality and increased levels of aspartate aminotransferase (ALT), alanine aminotransferase (AST), lactate, proBNP, Patent Cooperation Treaty (PCT), C-reactive protein (CRP), ferritin, and D-dimer ($p < 0.001$), Table 3.

Table 3: Association between mortality and laboratory data

Laboratory data	Mortality, mean \pm SD		P
	Nonsurvivor (n = 28)	Survivor (n = 32)	
TLC	9.68 \pm 2.86	7.47 \pm 2.15	0.008*
Hb	10.48 \pm 2.24	12.06 \pm 1.51	0.002*
Lymphocyte	1.03 \pm 0.25	1.02 \pm 0.28	0.978
PLTs	179.71 \pm 51.93	251.91 \pm 65.28	0.003*
Creatinine (mg/dl)	1.83 \pm 0.50	1.30 \pm 0.32	0.063
ALT (U/L)	51.79 \pm 13.86	39.69 \pm 9.89	< 0.001**
AST (U/L)	79.71 \pm 20.10	59.13 \pm 16.67	< 0.001**
Lactate	5.62 \pm 1.14	2.58 \pm 0.56	< 0.001**
Pro BNP (pg/ml)	189.75 \pm 36.56	121.91 \pm 30.99	< 0.001**
PCT (ng/ml)	2.09 \pm 0.59	0.98 \pm 0.27	< 0.001**
CRP (mg/l)	179.54 \pm 26.91	114.31 \pm 24.07	< 0.001**
Ferritin (ng/ml)	355.18 \pm 77.64	235.00 \pm 54.30	< 0.001**
LDH (U/L)	557.68 \pm 105.83	510.94 \pm 95.80	0.078
D-Dimer (mg/mL)	4.17 \pm 1.18	1.88 \pm 0.55	<0.001**

$p > 0.05$ NS, * $p < 0.05$ S, ** $p < 0.001$ HS. SD: Standard deviation, S: Significant, HS: Highly significant, PLTs: Platelets, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, ALT: Alanin Transaminase, PCT: Procalcitonin, CRP: C-reactive protein.

There was statistically significant association between mortality and RV function regarding TAPSE ($p = 0.031$), RV basal diameter ($p = 0.022$), and expiratory positive airway pressure (EPAP) ($p = 0.038$). There was a highly statistically significant association between mortality and FAC % ($p < 0.001$), Table 4.

Table 4: Association between mortality and echocardiography data (n = 60)

Echocardiography data	Mortality		P
	Nonsurvivor (n = 28)	Survivor (n = 32)	
LV function, mean \pm SD			
EF %	63.64 \pm 8.39	65.41 \pm 7.09	0.381
RV function, mean \pm SD			
TAPSE	1.82 \pm 0.41	2.18 \pm 0.62	0.031*
FAC %	29.75 \pm 7.90	40.38 \pm 9.47	< 0.001**
RV basal diameter	4.09 \pm 0.91	3.53 \pm 0.92	0.022*
EPAP	31.54 \pm 9.35	24.56 \pm 6.99	0.038*
TR, n (%)			
No	1 (3.6)	1 (3.1)	0.163
Mild	12 (42.9)	18 (56.3)	
Moderate	11 (39.3)	13 (40.6)	
Severe	4 (14.3)	0	

$p > 0.05$ NS, * $p < 0.05$ S, ** $p < 0.001$ HS. SD: Standard deviation, S: Significant, HS: Highly significant, LV: Left ventricular, RV: Right ventricular, TAPSE: Tricuspid plane systolic excursion, FAC: Fractional area change, EF: Ejection fraction, EPAP: Estimated Pulmonary Artery Pressure, TR: Tricuspid Regurgitation.

Discussion

In COVID-19 acute respiratory distress syndrome, Bleakley *et al.* [7] described the basic phenotype and clinical associations of RV impairment and ARDS. They found that the mean RV systolic function defined by RV FAC ($28.9\% \pm 10.6\%$) was reduced while

the mean TAPSE was (20 ± 4.8 mm). Mechanisms underlying COVID-19-related RV damage include increased RV afterload and decreased RV contractility due to several factors such as acute respiratory distress syndrome, pulmonary vascular thrombosis, direct viral myocardial damage, hypoxia, inflammatory response, and autoimmune damage. Segmental wall motion abnormality or global hypokinesia at the right ventricle might develop in COVID-19 [8]. Right chambers tolerate preload augmentation worse than their left counterparts. Thus, high RV pressure produces RV myocardial stress and troponin release [9].

Puntmann *et al.* [10] cohort study included 100 patients recently recovered from COVID-19 to explore the cardiovascular effects. They reported that patients with COVID-19 had a lower RV ejection fraction than healthy controls.

According to Li *et al.* [11], patients with COVID-19 pneumonia had slightly lower TAPSE. Furthermore, the TAPSE was slightly lower in critically ill patients ($P = 0.0128$) than in severely ill patients. A decreased TAPSE (< 17 mm) was found in three (8.6%) moderate and five (35.7%) critically-severe patients [12]. The American Society of Echocardiography recommends routinely using (TAPSE) to evaluate the RV systolic function; a low TAPSE value may be considered an earlier manifestation of cardiac involvement or complications in COVID-19 patients [13].

When comparing alive and dead patients in D'Alto *et al.*, [14] study investigated the prevalence and prognostic impact of right heart failure and RV-arterial uncoupling in COVID-19 complicated by ARDS. The mean TAPSE (mm) in alive was (25 ± 4) versus (19 ± 4) in dead.

In our study, there was a statistically significant association between mortality and total comorbidities ($p = 0.038$).

Furthermore, there was a significant association between clinical comorbidities and disease severity in Liaqat *et al.* [15] research aimed to investigate the myocardial injury patterns, ECG changes, echocardiographic parameters in COVID-19, which included diabetes, hypertension, obesity, and smoking ($p < 0.001$). Patients with COVID-19 disease who have comorbidities, such as hypertension or diabetes mellitus, are more likely to develop a more severe course and progression of the disease [16]. Comorbidity may also relate to reduced immune function. Downregulation of immune function may expect to occur in these patients and may increase the risk of mortality eventually [17].

Results of the present study showed a statistically significant association between mortality and increased TLC ($p = 0.008$), lower Hb ($p = 0.002$), and decreased PLTs ($p = 0.003$); there was a highly statistically significant association between mortality and increased levels of ALT, AST, lactate, proBNP, PCT,

CRP, ferritin, and D-dimer ($p < 0.001$).

Deaths had higher levels of white blood count (WBC), monocyte, d-dimer, ALT, complete bilirubin, lactate dehydrogenase, creatine kinase, blood urea nitrogen, creatinine, hypersensitive troponin I, and procalcitonin (all $p < 0.05$) in Zou *et al.*, [18] retrospective observational cohort included 154 COVID-19 patients. Patients with COVID-19 pneumonia may have normal, low, or high leukocyte counts. Cytokine storm and the use of granulocyte colony-stimulating factor for the leukopenia associated with SARS-CoV-2 may worsen the condition [19]. Lymphopenia and increased WBC count may be associated with increased (CRP) and mortality [20].

In addition to liver involvement, AST also increases when other organs are involved, as well [21]. As a result, in addition to damaging the liver, an increased level of AST may indicate damage to other organs, making the patient experience even worse consequences when this enzyme rises. Thus, a worse prognosis can be expected in people with COVID-19 when AST is elevated in comparison to cases with elevated ALT [22].

Thrombocytopenia was associated with an increased risk of in-hospital mortality in patients with COVID-19 in the study by Yang *et al.* [23]. The lower the platelet count, the higher the mortality becomes. Platelets are believed to be the first responders in innate immunity and can interact with pathogens including bacteria and viruses through multiple platelet surface receptors. The decrease in platelet was associated with poor respiratory function in critically ill patients. Platelets directly interact with viral pathogens through the pathogen recognition receptors such as protease-activated receptor 4 and glycoprotein IIIa, and this interaction can lead to platelet activation, which is associated with lung inflammation as well as the severity of viral infections, lung injury, and death [24].

Results of the current study showed statistically significant association between mortality and RV function regarding TAPSE ($p = 0.031$), RV basal diameter ($p = 0.022$), and EPAP ($p = 0.038$). There was a highly statistically significant association between mortality and FAC % ($p < 0.001$).

In agreement with our results, Li *et al.*, [25] investigated the right heart function in (COVID-19) patients with acute respiratory distress syndrome (ARDS); they found that RVFAC and TAPSE were associated with higher mortality. Martha *et al.* [26] assessed the association between (TAPSE) and mortality in (COVID-19). Each 1 mm decrease in TAPSE was associated with increased mortality. TAPSE was shown to be associated with the occurrence of pulmonary embolism in patients with COVID-19 [26].

Diaz-Arocutipa *et al.* [27] found that RV dysfunction was independently associated with an almost threefold increase in mortality in COVID-19 patients;

each 1% decrease in FAC was significantly associated with higher mortality.

Conclusion

In COVID-19 patients, RV function must be assessed and its prognostic importance recognized. RV dysfunction is not only a symptom of high pulmonary pressures, but it also contributes to cardiac insufficiency.

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