

Early Bedside Predictors of Cardiac Involvement in COVID-19

Amr Setouhi*, Gamal Fathy, Tarek Abdelrahman, Khaled Mahmoud

Cardiology Department, Faculty of Medicine, Minia University, Minia, Egypt

*Corresponding author: Amr Setouhi, Mobile: (+20)1010635356, E-Mail: amr_setouhi@yahoo.com

ABSTRACT

Background: COVID-19 could lead to severe acute respiratory syndrome leading to myocardial injury. It is associated with high morbidity and mortality. COVID-19 progression severity can be predicted by cardiac signs. Biomarkers can be used for early detection of cardiac injury and damage and prediction of severe prognosis ultimately. Echocardiography is used for therapeutic management and diagnostic procedures for COVID-19 patients. Detection of subtle cardiac damage early allows for providing efficient treatment.

Objective: The aim of the current study was to predict early cardiac involvement in COVID-19 depending on different laboratory and echocardiographic parameters.

Patients and methods: This prospective analytical observational study included a total of 100 patients diagnosed as positive COVID-19, depending on polymerase chain reaction 'PCR' of nasopharyngeal swabs. Patients underwent full echocardiographic assessment, electrocardiogram (ECG) and laboratory investigations just upon admission. Further grouping of patients according to clinical deterioration was done to detect the prognostic value of investigations.

Results: Group I of clinically deteriorated patients had more lymphopenia (mean \pm SD: $954.2 \pm 6.5 \times 10^9$ /l), higher neutrophils-lymphocytic ratio (mean \pm SD: 3.9 ± 0.2), less TAPSE (tricuspid annular plane systolic excursion) (mean \pm SD: 14.85 ± 3.29 mm) and more basal RV (right ventricle) diameter (mean \pm SD: 39.93 ± 3.08 mm) in comparison with clinically stable patients. Deterioration of TAPSE (p value = 0.017) & basal RV diameter (p value = 0.044) were found to have significant relation with grading of respiratory failure using PO₂/FiO₂ ratio which had significant positive correlation with RV diameter (p value = <0.001 and r = 0.357).

Conclusions: TAPSE & basal RV diameter can early predict cardiac involvement in COVID 19 disease and have the prognostic ability to predict the degree of respiratory failure in deteriorated patients.

Keywords: COVID 19, Coronavirus, Acute respiratory syndrome, Transthoracic echocardiography.

INTRODUCTION

Coronavirus disease (COVID-19) is initiated as a result of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It belongs to the vast family of viruses recognized as coronaviruses. COVID-19 is a positive-sense single-stranded RNA (+ ssRNA) virus, distinguished by a single linear ribonucleic acid (RNA) segment containing around 30,000 bases long ⁽¹⁾.

The SARS-CoV-2 virion diameter is 50–200 nanometres consisting of 4 different structural proteins. The structural proteins are the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins ⁽²⁾. The S1 subunit facilitates the virus attachment, and the S2 subunit plays a role in virus fusion ⁽³⁾.

The SARS-CoV-2 harbors the virus for long periods without pathogenic effects. It can be transmitted while patients are symptomatic. Developing symptoms usually takes two days ⁽⁴⁾. Yet patients stay infectious in severe and moderate cases for two weeks and 7 to 12 days, respectively ⁽⁵⁾. Airborne transmission happens especially in very overcrowded or poorly ventilated closed areas ⁽⁶⁾. Infection may take place if patients are subjected to contaminated surfaces followed by eyes, nose, or mouth touch with contaminated hands, but this is not decisively confirmed ⁽⁷⁾.

SARS-CoV-2 respiratory failure affects the brainstem and invades the central nervous system (CNS)⁽⁸⁾. The peripheral nerve invasion is attributed to the low levels of angiotensin-converting enzyme 2

(ACE2) in the brain leading to chronic damage to the cardiovascular system and acute myocardial injury. The high rates of cardiovascular symptoms are due to immune system disorders caused by the systemic inflammatory response as disease progression. The percentage of thrombosis and venous thromboembolism is 31% and 25%, respectively. This high percentage detected in ICU COVID-19 patients is attributed to the poor prognosis ⁽⁹⁾. The high D-dimer levels indicate that mortality is due to blood vessel dysfunction and clot formation. Blood vessel constriction is observed inside the pulmonary circulation causing a reduction in the oxygenation process. Around 30% of the deaths were attributed to kidney complications ^(10,11).

Classical serum biomarkers of Cytokine release syndrome (CRS) are observed in COVID-19 and acute respiratory distress syndrome patients causing a higher C-reactive protein (CRP), ferritin and lactate dehydrogenase (LDH)^(12,13). Pathogenic granulocyte macrophage-colony stimulating factor (GM-CSF) discharges T-cells relative to the inflammatory interleukin-6 (IL-6) occurrence leading to secreting monocytes and severe lung pathology ⁽¹⁴⁾. The inflammatory cytokines and other systemic inflammation markers increase refer to a hyper-inflammatory state ⁽¹⁵⁾. Several organs may be subjected to inflammation and followed by dysfunction of the endothelium due to the infection of endothelial cells and the host inflammatory response ^(16,17).

Myocardial involvement was found in 20-30% of hospitalized COVID-19 patients⁽¹⁸⁾. A single case was reported for acute pericarditis and left ventricular dysfunction without presence of respiratory tract signs/ symptoms⁽¹⁹⁾.

ACE2 receptors are the functional receptors for COVID-19 in the heart and lungs^(20, 21). The American heart association recommended maintaining ACE inhibitors in patients with heart failure, myocardial infections or hypertension. Several review articles indicated that rennin-angiotensin-aldosterone system inhibitor withdrawal is determinantal in COVID-19 patients⁽²²⁾.

In Wuhan, China, reports indicated that 23% of COVID-19 patients were subjected to heart failure due to exacerbation of preexisting left ventricular dysfunction or new cardiomyopathy⁽²²⁾. A higher expansion of the small pulmonary veins and lung lesions was observed in heart failure. Effective anti-failure treatment improved the clinical conditions remarkably⁽²³⁾.

The cardiac injury increases the mortality to 51.2% compared to general COVID-19 patients with a mortality rate of 4.5%⁽²⁴⁾.

The proposed treatments include antiviral medications. Around 90% of 138 COVID-19 patients were successfully treated using antiviral medications⁽²⁴⁾. Antiviral drugs may cause cardiac insufficiency, arrhythmias and other cardiovascular disorders. So, cardiac injuries caused by antiviral treatments should be considered^(24, 25).

Patients may develop overt cardiovascular abnormalities. After recovering from cardiac injuries, patients are expected to suffer from cardiomyopathy and cardiac arrhythmias. 68, 60, and 4% of the recovered patients suffered from hyperlipidemia, glucose metabolism disorders and cardiovascular system abnormalities, respectively. Several studies on the SARS-CoV chronic cardiac outcomes (which have a similar structure to SARS-CoV-2) indicated that chronic cardiac issues after recovery must be considered^(23, 24).

Biomarkers should be measured once the patient is admitted to the hospital for cardiac damage to detect cardiac injury and possible severe prognosis. Recent evidence shows that cardiac signs can be used as factors to distinguish the progression of the mild versus severe COVID-19⁽²⁴⁾.

Using transthoracic echocardiography (TTE) will help significantly to diagnose myocarditis, acute coronary syndromes, acute left/right ventricular failure and secondary myocardial damage either due to mechanical ventilation or sepsis offering a noninvasive assessment⁽²⁶⁾. Myocardial function in systole and diastole can be quantified using transthoracic echocardiography (TE). Pulsed-wave Doppler measurements left ventricular ejection fraction, and RV parameters are common measures that can provide substantial data on cardiac function⁽²⁷⁾.

The aim of the current study was to predict early cardiac involvement in COVID-19 depending on different laboratory and echocardiographic parameters.

PATIENTS AND METHODS

This prospective analytical observational study included a total of 134 patients diagnosed as positive COVID-19, depending on polymerase chain reaction 'PCR' of nasopharyngeal swabs, admitted to the quarantine of Minia University Hospital. This study was conducted between December 2019 to December 2020.

Patients underwent full echocardiographic assessment, electrocardiogram (ECG) and laboratory investigations just upon admission. 34 ones were excluded due to previous cardiovascular diseases. Consequently, 100 patients were involved in the study. The clinical course of the included ones during hospital stay was carefully recorded to determine which of the investigations can early predict cardiac involvement of COVID illness.

Inclusion criteria:

- Patients with a positive swab for COVID-19.

Exclusion criteria:

- 1- Patients previously known to have structural heart disease.
- 2- Patients <18 years old.
- 3- Known chest diseases, previous pulmonary embolism or another infarction.

According to the clinical course of the included 100 patients during the hospital stay, they were divided into:

- Group I: 46 patients who developed clinical deterioration and needed mechanical ventilation or circulatory support.
- Group II: 54 patients who did not need mechanical ventilation or circulatory support.

All the participants were subjected to the following:

- 1- Brief history survey (how old and comorbidities).
- 2- Clinical examination.
- 3- Different cardiac-specific and non-specific laboratory and imaging parameters were used for following up COVID-19-positive patients and predicting if they developed deterioration of their clinical status. Deterioration is defined by the need for mechanical ventilation or vasopressor therapy.

The laboratory parameters included:

- **Non-specific:** Complete blood count (CBC).
- **Specific:** Highly sensitive cardiac Troponin (Hs- cTnT), creatinekinase (CK-MB), and arterial Blood Gases (ABG).

4- Transthoracic echocardiography:

All participants in this study were subjected to

transthoracic echocardiography by a well-qualified operator who was blinded by the data of both groups. Echocardiography was made by using SIEMENS ACUSON SC 2000 ultrasound (Germany, Siemens) using the dedicated probe (4V1 probe). Standard gray scale 2D images came out at a frame rate of 50–90 frames/s during four consecutive cardiac cycles and software package (velocity vector imaging VB10D, Siemens).

The imaging parameters obtained by transthoracic echocardiography included:

- Left ventricle (LV) systolic function.
- LV diastolic function.
- Right ventricle (RV) systolic function by TAPSE.
- Pulmonary artery systolic pressure (PASP).
- Basal RV diameter.

Ethical consent:

The study was ethically approved by the Research Ethics Committee (FMREC), Faculty of Medicine, Minia University, Minia, Egypt (date: 08.2020, decision No. 673: 2020). The FMREC is constituted and operating according to ICH-GCP

guidelines and applicable local and institutional regulations and guidelines which govern EC operations. Written informed consent of all the patients (legal guardians) was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The Statistical Package for the Social Sciences Software (SPSS version 25.0; IBM corp., Armonk, New York, USA) was used to analyze the results. Continuous variables were used as the mean ± SD, whereas categorical variables appear to be frequencies and percentages. Pearson’s r correlation analysis was used to assess the links between variables. P less than or equal to 0.001 was considered a highly expressive value. While p less than or equal to 0.05 was accepted as statistically significant with a confidence interval (CI) greater than 95%.

RESULTS

The results showed that no statistically significant variance was observed between the two groups counting on age, sex, diabetes, or being hypertensive (Table 1).

Table (1): Comparison between Group I and Group II counting on demographic and Co-morbidities.

		Group I n = 46	Group II n = 54	P-value	Sig.
Age (years)	Mean ± SD	53.93 ± 15.00	55.59 ± 15.81	0.594	NS
Sex	Male	24 (52.2%)	20 (37.0%)	0.129	NS
	Female	22 (47.8%)	34 (63.0%)		
Diabetes		21 (45.7%)	26 (48.1%)	0.803	NS
Hypertensive		21 (45.7%)	31 (57.4%)	0.241	NS

P-value < 0.01: highly significant (HS); P-value > 0.05: Non-significant (NS); and P-value < 0.05: Significant (S). *: Chi-square test, •: Independent t-test. n: number, %: percentage, SD: Standard deviation, Sig.: significance.

Table (2) shows the laboratory difference between the two studied groups. Regarding blood film parameters, lymphopenia was more in group I vs group II (mean ± SD: 954.2± 6.5 vs 1600± 9.5) (p-value = 0.006). As a consequence, the NL ratio was higher in group I (mean ± SD: 3.9± 0.2) in comparison to group II (mean ± SD: 2.8± 0.5) (p-value = 0.012). In addition, the two groups showed no significant difference in troponin, D dimer, and CKMB values.

Table (2): Comparison between group I and group II considering laboratory data.

		Group I No. = 46	Group II No. = 54	P-value	Sig.
TLC	Mean ± SD	9.33 ± 2.95	9.20 ± 2.15	0.904	NS
Lymphocytic count (x10 ⁹ /l)	Mean ± SD	954.2± 6.5	1600± 9.5	0.006	HS
NL ratio	Mean ± SD	3.9± 0.2	2.8± 0.5	0.012	S
Troponin (ng/mL)	Mean ± SD	132.98 ± 8.53	140.69 ± 7.54	0.616	NS
D dimer (ng/ml)	Mean ± SD	818.67 ± 53.50	690.43 ± 66.20	0.079	NS
CK-MB (IU/L)	Mean ± SD	12.04 ± 2.22	13.70 ± 2.62	0.269	NS

P-value < 0.01: highly significant (HS); P-value > 0.05: Non-significant (NS); and P-value < 0.05: Significant (S). *: Chi-square test, •: Independent t-test. n: number, %: percentage, SD: Standard deviation, Sig.: significance, TLC: total leucocytes count, NL ratio: neutrophils lymphocytic ratio, CKMB: Creatine kinase.

By examining the patients, table (3) shows that no statistically significant differences was observed between the two study groups considering, the measured LVEF, diastolic function and pulmonary hypertension. However, TAPSE was significantly lesser in Group I (Mean ± SD: 14.85 ± 3.29 mm) than in Group II (Mean ± SD: 19.35 ± 4.01 mm) (p-

value = 0.02). RV was impaired in 73.9% of the patients in Group I and 20.3% of Group II patients (p-value = 0.007). Also, basal RV diameter was smaller in Group II than in Group I, and this difference was statistically significant. In Group I, the basal RV diameter was about 39.93 ± 3.08 mm while in Group II it was about 38.67 ± 2.82 mm (p-value = 0.034). The basal RV diameter was > 41 mm in 54.3% of the patients in Group I and 27.8% of Group II patients (p-value = 0.006).

Table (3): Comparison between group I and group II considering echocardiographic parameters.

		Group I	Group II	p-value
		n= 46	n= 54	
LVEF%	Mean ± SD	53.48 ± 10.77	50.17 ± 13.18	0.177
Diastolic function	Normal diastolic function	12 (52.2%)	11 (47.8%)	0.818
	Grade I LV DD	14 (43.8%)	18 (56.3%)	
	Grade II LV DD	9 (39.1%)	14 (60.9%)	
	Grade III LV DD	11 (50%)	11 (50%)	
TAPSE	Mean ± SD	14.85 ± 3.29	19.35 ± 4.01	0.02
	Less than 18mm	34 (73.9%)	11 (20.3%)	0.007
	More than 18mm	12 (26.1%)	43 (79.7%)	
Pulmonary hypertension	Present	24(52.17%)	25(46.2)	0.93
	Absent	22(47.83%)	29(53.8)	
Basal RV diameter	Mean ± SD	39.93 ± 3.08	38.67 ± 2.82	0.034*
	< 41mm	21 (45.7%)	39 (72.2%)	0.006*
	> 41mm	25 (54.3%)	15 (27.8%)	

P-value < 0.01: highly significant (HS); P-value > 0.05: Non-significant (NS); and P-value < 0.05: Significant (S). *: Chi-square test, •: Independent t-test. n: number, %: percentage, SD: Standard deviation, Sig.: significance, LVEF: left ventricle ejection fraction, LV DD: left ventricle diastolic dysfunction, TAPSE: tricuspid annular plane systolic excursion, RV: right ventricle.

Group, I COVID patients were critically ill, clinically deteriorated, and needed mechanical ventilation and/or circulatory support.

ABG analysis was frequently done to follow up the circulatory status and make the suitable changes in the ventilator setting or rates and type of circulatory support infusion. Initial ABG analysis (just upon ventilation and/or circulatory support) was used as a determinant of the clinical deterioration. PO₂/FiO₂ (P/F ratio) which is a strong objective tool to identify acute hypoxic respiratory failure, was used to classify group II into 3 subgroups; 1) Subgroup A: Patients with a P/F ratio (< 200) who are considered to have critical respiratory failure, 2) Subgroup B: Patients with P/F ratio (200-300) who are considered to have severe respiratory failure, 3) Subgroup C: Patients with P/F

ratio (>300) who are considered to have mild respiratory failure. Then we compared the 3 groups regarding the echocardiographic levels of TAPSE and RV dilatation as shown in table (4).

In group I, ARDS was more prevalent in patients with RV dysfunction. All patients of subgroup A with critical respiratory failure had 100% deterioration of TAPSE < 18 mm, while subgroup B with severe respiratory failure had incidence of TAPSE deterioration <18 mm (38.1%). Half the number of mild respiratory failure patients developed TAPSE deterioration >18mm (p-value = 0.017). RV dilatation >41mm was more in subgroup B and C of severe and mild respiratory failure (66.7% and 50%, respectively) in comparison with subgroup A of critical respiratory failure (14.3%) (p-value=0.044).

Table (4): Comparison between group I subgroups regarding the deterioration of TAPSE and RV Grade

P/F ratio		Subgroup A		Subgroup B		Subgroup C		P-value	Sig.
		No.	%	No.	%	No.	%		
Deterioration of TAPSE	Less than 18mm	7	100.0%	8	38.1%	9	50.0%	0.017*	S
	More than 18mm	0	0.0%	13	61.9%	9	50.0%		
RV Diameter	< 41 mm	6	85.7%	7	33.3%	9	50.0%	0.044*	S
	> 41 mm	1	14.3%	14	66.7%	9	50.0%		

P-value > 0.05: Non-significant (NS); P-value < 0.05: Significant (S); P-value < 0.01: highly significant (HS). *: ANOVA test. n: number, %: percentage, SD: Standard deviation, Sig.: significance, P/F ratio: PO2/FiO2, TAPSE: tricuspid annular plane systolic excursion, RV: right ventricle.

Table (5) shows the correlations of the grade of respiratory failure by P/F ratio with important measured echocardiographic parameters. Significant positive correlation between P/F ratio and TAPSE as well as RV diameter (p= 0.044 as well as p<0.001 respectively).

Table (5): Correlation between P/F ratio of group I and (TAPSE, RV Diameter, and PASP)

	r	p- value
TAPSE	0.202	0.044
RV diameter	0.357	<0.001
PASP	-0.134	0.183

TAPSE: tricuspid annular plane systolic excursion, RV: right ventricle, PASP: Pulmonary artery systolic pressure.

DISCUSSION

COVID-19 is a pandemic infection detected in more than 1.8 billion people around the world, The pandemic overwhelmed health care systems due to the high demand for hospitalization and mortality rates (28).

COVID-19 is considered a global healthcare system crisis associated with the life-threatening SARS-CoV-2 (27). COVID-19 infection is associated with pulmonary lesions with severe symptoms. However, the infection may lead to considerable complications for other organs, such as the liver, heart, and spleen. It was reported that patients were admitted for cardiovascular symptoms, which may develop into heart injury in around 10% of the cases under study(28).

As a lesson learned from previous influenza epidemics, the deaths due to cardiovascular (CV) problems were more than those reported for pneumonia/influenza complications. Significant cardiovascular complications are expected in COVID-19 patients considering the high inflammatory burden of COVID-19. It was shown in a previous study that myocardial involvement was observed in around 20% – 30% of COVID-19 patients (26). The mechanism of

COVID-19 cardiac involvement is not yet well understood. However, studies have shown that COVID-19 cardiac involvement increased the risk of asymptomatic myocardial injury, acute coronary

syndrome, stress cardiomyopathy mild to fulminant myocarditis and cardiogenic shock(28).

In this study, we divided patients according to whether they were clinically deteriorated or not, into two groups, group I who had clinical deterioration, and group II who did not have clinical deterioration.

This study aimed to early detect whether the severity of COVID-19 infection is associated with cardiac involvement based on variable echocardiographic abnormalities and laboratory biomarkers.

As regards laboratory biomarkers, the current study demonstrated that among the different biochemical markers, lymphopenia was more in the clinically deteriorated group I vs group II (p-value = 0.006) and consequently more NLR in group I (p-value = 0.012).

In agreement with that, **Yang et al.**(29) reported similar results in a study including 93 patients with laboratory-confirmed COVID-19 who had undergone NLR, platelet-to-lymphocyte ratio (PLR), and CRP. They found that elevated NLR can be taken as independent biomarkers for showing a lack of efficient clinical findings in COVID-19.

Also, in concordance with our results, a review of literature and meta-analysis by **Huang et al.**(30) that analyzed data reported for COVID-19 adult patients in several articles focusing on lymphocyte count and other related results, like acute respiratory distress syndrome (ARDS), mortality, intensive care unit (ICU) care and COVID-19 severity. There was a total of 3099 patients from 24 studies, their meta-analysis refers to the poor outcomes in COVID-19 patients may lead to lymphopenia.

Our study included a very high-risk population who had needed hospital admission and found a clear statistical difference found between the two groups considering the incidence of RV systolic dysfunction (p = 0.006) and RV dilatation (p=0.007). Data have shown no considerable difference between the two groups considering the incidence of pulmonary hypertension (p=0.94).

Regarding the pathophysiological hypothesis, COVID-19 may lead to damage in the lung and acutely affect the RV and pulmonary pressures. The authors decided to evaluate if the TAPSE and RV diameter,

which are commonly used echocardiographic parameters, can play a prognostic role in hospitalized patients. Different mechanisms are defined for RV dysfunction including⁽³¹⁾: (1) systemic inflammation and hypoxemia inducing pulmonary vasoconstriction, (2) harming the pulmonary circulation through micro and/or macro thrombotic events, (3) high-flow oxygen or mechanical ventilation therapy promoting RV rise, (4) super-infection in combinations with other types of pneumonia leading to the alteration of the pulmonary ventilo-perfusive unit, (5) α -agonists use (in case of hemodynamic instability), (6) elevated left atrial pressure, owing to concomitant LV dysfunction causing elevated pulmonary pressures, and (7) a combination of all previous mechanisms.

Despite the consequences of RV pathophysiology, RV increase may result in hypotension and cardiac output reduction, with consequential impaired coronary perfusion triggering a “snake biting its tail” mechanism, for which RV dysfunction generates RV dysfunction⁽³¹⁾.

Also, in agreement with our study, a study by **Polito et al.**⁽³¹⁾, who had a look at 227 COVID-19 hospitalized patients and found that echocardiographic evidence of RV systolic dysfunction, may be useful to detect higher mortality risk for hospitalized COVID-19 patients.

Kim et al.⁽³²⁾ proposed that RV dilation or dysfunction increased the risk of death of hospitalized patients by more than 2-fold increase and still represents a significant risk in multivariate analysis, as indicated by an assessment conducted using standard clinical- and biomarkers, confirming the prognostic utility of RV remodeling evaluation in patients with COVID-19.

Also, in concordance with our results, **El-sayed et al.**⁽³³⁾, showed that RV dilatation was one of the chief abnormalities shown in 41% of the studied patients.

Another study by **Stockenhuber et al.**⁽³⁴⁾, compared the patients who survived & the patients who didn't survive considering basal RV diameter and they reported significant differences between both groups.

COVID-19 patients who suffer from cardiac injury should be treated considering RV dilatation, and poorer TAPSE, in comparison with patients without cardiac injury⁽³¹⁾. Remarkably, the RV impaired function is subjected to a higher mortality risk according to the right ventricle longitudinal strain (RVLS) assessment⁽³⁴⁾. In our register, conventional TTE parameters are collected and focused on more than RVLS, which was seldom reported. Certainly, the image's quality is an important factor on which the speckle-tracking echocardiography is dependent, this increases the difficulty of using the speckle-tracking echocardiography for ICU patients in supine or prone positions or on mechanical ventilation. In addition, using the speckle-tracking echocardiography effectively will require ECG-gating, adequate frame rate, and multiple cardiac cycles, acquired with similar heart rates. All these constraints are difficult to maintain

during the pandemic clinical context and may expose sonographers to higher infection risk⁽³²⁻³⁵⁾.

A published study demonstrated that the TTE evaluation of RV function and diameter is essential for COVID-19 patients, to classify the mortality risk. In our study, patients with lower TAPSE, and those with higher RV diameter, showed a higher possibility to develop in-hospital complications. Our analysis indicates that the intensive evaluation of echocardiographic is important for hospitalized COVID-19 patients to early diagnose and detect RV abnormalities.

Conventional echocardiographic parameters are used for the intensive evaluation of echocardiographic which is essential for the initial evaluation of the clinical management and critical/non-critical care setting and for identifying the COVID-19 long-term cardiac sequelae.

However, our findings suggested that there was no any significant difference regarding incidence of pulmonary hypertension between the two groups. Most patients in group I received mechanical ventilation. So, this finding may be owing to reduced pulmonary vascular resistance by positive pressure mechanical ventilation in those patients neutralizing increased PASP caused by increased pulmonary vascular resistance in COVID-19 pneumonia patients.

When we divided our patients in group I into three groups according to the P/F ratio, our results also demonstrated that RV dysfunction and RV dilatation are obvious clinical features in ARDS COVID-19 patients due to the COVID-19 severity and ARDS. In addition, an early RV function integrated assessment was detected using echocardiography by evaluating RV diameter and TAPSE. The RV function and cardiac activity in COVID-19 patients, as detected using echocardiographic parameters, indicate a certain degree of abnormality compared to normal healthy subjects⁽³⁵⁾.

Regarding RV diameter, despite relative less RV dilatation in critical ARDS which may be contributed to the rapid progression of the disease to death which was more rapid than the occurrence of RV dilatation, but significant RV dilatation was observed in severe and mild ARDS patients with relatively slower progression that allowed for dilatation occurrence.

In the current study, it was found that the critically severe group with severe ARDs developed a higher incidence of RV dysfunction, which is similar to previously reported findings of severe ARDS population with SARS and H1N1 viruses. Consequently, viral pneumonia patients are associated with RV dysfunction in severe ARDS patients. TAPSE, the most-widely RV function index, has been used globally for ARDS patients⁽³⁵⁾. As recommended by the American society of echocardiography (ASE) guidelines, the major RV dysfunction parameter is the < 18 mm TAPSE. In the present study, we found TAPSE less than 18 was significantly much higher in critically severe patients with ARDS than that in other patients in

group I, indicating that the presence of a correlation between the P/F ratio and RV dysfunction occurrence in critical COVID-19 patients.

The RV plays a major role in keeping pulmonary perfusion pressure and systemic venous pressure at regular levels for maintaining normal blood flow. The RV function is affected by many factors including impaired RV contraction and increased pulmonary vascular resistance. It is well known that the pulmonary vascular resistance increase may be found by hypoxemia, vasoconstrictor, hypercapnia, acidosis, and so on, which may cause the deterioration of right heart structure and function⁽³⁵⁾. The severe and critically severe COVID-19 patients are clinically characterized by severe hypoxemia increasing the resistance of the pulmonary vascular, and reduced ability of the right heart to normalize pressure⁽³⁵⁾. In this study, the right heart cavity was enlarged in COVID-19 patients.

The results observed in the current study showed that critically severe patients with ARDS have impaired RV systolic function, in concordance with what **Li et al.**⁽³⁵⁾ who observed that in a study of over 49 COVID-19 patients with ARDS who underwent TTE to assess cardiac cavity diameters, TAPSE, tricuspid valve regurgitation pressure gradient biggest (TRPG), PASP, minimum diameter (IVCmin), maximum inferior vena cava diameter (IVCmax) and inferior vena cava collapse index (ICV-CI). **Li et al.**⁽³⁵⁾ found that critically impaired severe COVID-19 patients with ARDS have impaired right ventricular function.

LIMITATIONS

The study was a retrospective study and the sample size was limited. The results still need to be further confirmed by prospective clinical studies. The right ventricular function protection and monitoring should be improved during COVID-19 patient management. In addition, although the assessment of echocardiography was performed by a cardiologist, the three-level of isolation and protection considered while contacting the COVID-19 patients increased the challenges of the examination process. However, echocardiography is the most reliable and trusted method in addition to examination for the clinical assessment of COVID-19 patients.

CONCLUSIONS

It could be concluded that COVID 19 patients who had cardiac manifestations have higher LN ratio, PO₂/FiO₂, Basal RV diameter, TAPSE & RV grade deterioration. Basal RV diameter could be employed as an indicator of evaluating cardiac affection in COVID 19 patients. PO₂/ FiO₂ may be related to both TAPSE and deterioration of RV grade in COVID patients with cardiac manifestations.

RECOMMENDATIONS

Thus, we recommend the usage of combined laboratory and echocardiographic parameters for prognostic purposes in patients with clinically deteriorated COVID-19 status during their hospital stay.

The most reliable laboratory parameters are lymphocytic count, NL ratio, PaO₂, PO₂/FiO₂ ratio, and O₂ saturation. The prognostic echocardiographic parameters are TAPSE and basal RV diameter.

Consent for publication: Not applicable.

Availability of data and materials: The dataset used during the current study is available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: No source of funding.

Authors' contributions: AMS, TMA and KSM designed the study. AMS, GMF and TMA recorded the data of the patients. AMS, GMS, TMA and KSM analyzed and interpreted the data. GMF and TMA have drafted the work. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

REFERENCES

1. **Akkiz H (2021):** Implications of the novel mutations in the SARS-CoV-2 genome for transmission, disease severity, and the vaccine development. *Frontiers in Medicine*, 8: 636532. <https://dx.doi.org/10.3389/fmed.2021.636532>
2. **Wu C, Liu Y, Yang Y et al. (2020):** Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, 10(5): 766-788.
3. **Huang Y, Yang C, Xu X et al. (2020):** Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacologica Sinica*, 41(9): 1141-1149.
4. **Verbeek J, Rajamaki B, Ijaz S et al. (2020):** Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff. <https://doi.org/10.1002/14651858.CD011621.pub4>
5. **Qiu H, Wu J, Hong L et al. (2020):** Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *The Lancet Infectious Diseases*, 20(6): 689-696.
6. **Li Y (2021):** Hypothesis: SARS-CoV-2 transmission is predominated by the short-range airborne route and exacerbated by poor ventilation. *Indoor Air*, 31(4): 921-26.
7. **Contini C, Caselli E, Martini F et al. (2020):** COVID-19 is a multifaceted challenging pandemic which needs urgent public health interventions. *Microorganisms*. 8(8):1228. <https://doi.org/10.3390/microorganisms8081228>.
8. **Li Y, Bai W, Hashikawa T (2020):** The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology*, 92(6): 552-555.
9. **Artifoni M, Danic G, Gautier G et al. (2020):** Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *Journal of Thrombosis and Thrombolysis*, 50(1): 211-216.

10. **Pourmand G, Salem S, Mehra A et al. (2007):** Infectious complications after kidney transplantation: a single-center experience. *Transplant Infectious Disease*, 9(4):302-309.
11. **Hamilton P, Hanumapura P, Castelino L et al. (2020):** Characteristics and outcomes of hospitalised patients with acute kidney injury and COVID-19. *PloS One*, 15(11): e0241544. <https://doi.org/10.1371/journal.pone.0241544>
12. **Farooqi F, Dhawan N, Morgan R et al. (2020):** Treatment of severe COVID-19 with tocilizumab mitigates cytokine storm and averts mechanical ventilation during acute respiratory distress: a case report and literature review. *Tropical medicine and infectious disease*, 5(3): 112-17.
13. **Sherwood E, Toliver-Kinsky T (2004):** Mechanisms of the inflammatory response. *Best Practice & Research Clinical Anaesthesiology*, 18(3): 385-405.
14. **Pallath M, Ahirwar A, Tripathi S et al. (2021):** COVID-19 and nutritional deficiency: a review of existing knowledge. *Hormone Molecular Biology and Clinical Investigation*, 42(2):1-9.
15. **Chen L, Hoiland R, Stukas S et al. (2020):** Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *European Respiratory Journal*, 56(4): 2003006. <https://doi.org/10.1183/13993003.03006-2020>
16. **Iwasaki M, Saito J, Zhao H et al. (2021):** Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: molecular mechanisms and implications. *Inflammation*, 44(1): 13-34.
17. **DeFilippis A, Chapman A, Mills N et al. (2019):** Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. *Circulation*, 140(20): 1661-1678.
18. **Gavriatopoulou M, Korompoki E, Fotiou D et al. (2020):** Organ-specific manifestations of COVID-19 infection. *Clinical and experimental medicine*, 20(4): 493-506.
19. **Ni W, Yang X, Yang D et al. (2020):** Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care*, 24(1):1-10.
20. **South A, Diz D, Chappell M (2020):** COVID-19, ACE2, and the cardiovascular consequences. *American Journal of Physiology-Heart and Circulatory Physiology*, 318(5): 1084-1090.
21. **Yancy C, Jessup M, Bozkurt B et al. (2016):** 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*, 68(13): 1476-1488.
22. **Chang W, Toh H, Liao C et al. (2021):** Cardiac involvement of COVID-19: a comprehensive review. *The American Journal of the Medical Sciences*, 361(1): 14-22.
23. **Yao X, Ye F, Zhang M et al. (2020):** In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*, 71(15): 732-739.
24. **Aghagholi G, Gallo Marin B, Soliman L, Sellke F (2020):** Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. *Journal of Cardiac Surgery*, 35(6): 1302-1305.
25. **Mitrani R, Dabas N, Goldberger J (2020):** COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm*, 17(11): 1984-1990.
26. **Cameli M, Pastore M, SolimanAboumarie H et al. (2020):** Usefulness of echocardiography to detect cardiac involvement in COVID-19 patients. *Echocardiography*, 37(8): 1278-1286.
27. **Lassen M, Skaarup K, Lind J et al. (2020):** Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Heart Failure*, 7(6): 4189-4197.
28. **Tersalvi G, Vicenzi M, Calabretta D et al. (2020):** Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. *Journal of Cardiac Failure*, 26(6): 470-475.
29. **Yang A, Liu J, Tao W et al. (2020):** The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *International Immunopharmacology*, 84: 106504. <https://doi.org/10.1016/j.intimp.2020.106504>
30. **Huang I, Pranata R (2020):** Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *Journal of Intensive Care*, 8(1): 1-10.
31. **Polito M, Silverio A, Di Maio M et al. (2021):** Prognostic Implications of Right Ventricular Function and Pulmonary Pressures Assessed by Echocardiography in Hospitalized Patients with COVID-19. *Journal of Personalized Medicine*, 11(12): 1245. <https://doi.org/10.3390/jpm11121245>
32. **Kim J, Volodarskiy A, Sultana R et al. (2020):** Prognostic utility of right ventricular remodeling over conventional risk stratification in patients with COVID-19. *Journal of the American College of Cardiology*, 76(17): 1965-1977.
33. **Mahmoud-Elsayed H, Moody W, Bradlow W et al. (2020):** Echocardiographic findings in patients with COVID-19 pneumonia. *Canadian Journal of Cardiology*, 36(8): 1203-1207.
34. **Stockenhuber A, Vrettos A, Androschuck V et al. (2021):** A pilot study on right ventricular longitudinal strain as a predictor of outcome in COVID-19 patients with evidence of cardiac involvement. *Echocardiography*, 38(2): 222-229.
35. **Li Y, Zheng J, Jin Y et al. (2020):** Acute right ventricular dysfunction in severe COVID-19 pneumonia. *Reviews in Cardiovascular Medicine*, 21(4): 635-641.