

ORIGINAL RESEARCH

Association of Echocardiographic Findings with in-Hospital Mortality of COVID-19 Patients and Their Changes in One-Month Follow-Up; a Cohort Study

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Abstract: **Introduction:** Evidence showed that cardiac complications may occur in coronavirus disease-19 (COVID-19) during the acute and post-infection phases. This study aimed to evaluate the association between the echocardiographic characteristics and in-hospital mortality of COVID-19 patients as well as the changes after one-month follow-up. **Methods:** All adult (≥ 18 years old) hospitalized COVID-19 patients in need of echocardiography based on the guideline of the Iranian Society of Echocardiography for performing various types of echocardiography during the COVID-19 pandemic were included in this study. An expert cardiologist performed the echocardiography on all patients and also on all available patients one month after discharge. **Results:** 146 hospitalized cases of COVID-19 and 81 cases available for 1-month follow-up echocardiography were studied in this prospective study. Left ventricle wall hypokinesia, aorta valve stenosis, dilated Inferior Vena Cava (IVC), and Pulmonary Artery Systolic Pressure (PASP) of more than 35 were associated with 3.59 (95% CI: 1.19-10.79, $p = 0.02$), 11 (95% CI: 3.3 – 36.63, $p = 0.001$), 5.58 (95% CI: 1.04-29.41, $p = 0.041$), and 2.91 (95% CI: 1.35 – 6.3, $p = 0.001$) times higher odds of mortality than healthy subjects. In 1-month follow-up of patients, deterioration in LVEF ($p = 0.03$) was detected in the not-fully vaccinated patients, and a significant decrease in PASP was observed in all cases ($p = 0.04$); but these changes were not clinically important. **Conclusion:** Left ventricle wall hypokinesia, aorta valve stenosis, dilated IVC, and PASP ≥ 35 were predictors of in-hospital mortality in our study. There were not any potential clinically significant differences in one-month echocardiographic follow-ups of the studied patients.

Keywords: COVID-19; Echocardiography; Prognosis; Mortality; SARS-CoV-2

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1. Introduction

Since the start of the coronavirus disease-19 (COVID-19) pandemic in late 2019, to August 5, 2022, the virus has spread to 228 countries and territories and caused 6 million deaths in less than 3 years (1). Iran was one of the first countries to become involved in this pandemic and is one of the top 20 countries with the greatest number of COVID-19 patients

(2, 3). Although the respiratory system is the main organ involved in COVID-19 infection, there is strong evidence that the virus responsible for this disease (SARS-CoV-2) can affect various organs, such as the heart, due to its receptor, angiotensin converting enzyme 2 (ACE2) (4).

The cardiac manifestations of COVID-19, as important causes of its morbidity and mortality (5), vary from asymptomatic increases in cardiac biomarkers (6). The virus could injure the heart directly, due to myocarditis or infarction, or indirectly, due to shock or pulmonary complications (6). Also, previous studies introduced cardiac complications such as myocardial fibrosis and arrhythmia as sequelae of long-term COVID-19 (7).

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Echocardiography is a valuable tool for assessment of the cardiovascular system during COVID-19 infection, because it is generally available, affordable, and can provide useful clinical information that could even impact the treatment strategies of the patients (8). Most previous echocardiographic studies assessed the cardiac characteristics of infected patients during hospitalization. They demonstrated a range of cardiac complications, including left ventricular (LV) and right ventricular (RV) dysfunctions during the acute phase of COVID-19 (6, 8-11). These characteristics have been demonstrated to be potential independent predictors of prognosis (7, 9). Also, few studies evaluated post-infection cardiac complications and their related changes in echocardiography (12-14). Evidence shows individuals with COVID-19 are more likely to develop cardiovascular diseases of various types after the first 30 days following infection (15). Due to the need to assess baseline echocardiographic characteristics of the patients as a significant factor in prognosis and the lack of follow-up studies in Iran, we conducted this study to evaluate the association between the echocardiographic characteristics and in-hospital mortality of COVID-19 patients as well as the changes after one-month follow-up.

2. Methods

2.1. Study design and setting

This prospective cohort study was conducted from January 2022 to July 2022 at Imam Reza Educational Hospital, Tehran, Iran. The data of each COVID-19 patient was checked from hospitalization to discharge or in-hospital mortality. Also, one month after discharge from the hospital, patients were referred to the hospital's cardiology clinic for follow-up echocardiography. All diagnostic and treatment processes were based on the latest version of the national COVID-19 protocol. Before the start of data gathering, the Ethical Committee of AJA University of Medical Sciences approved the study protocol (IR.AJAUMS.REC.1400.261). The researchers acquired written informed consent and followed the recommendations in Helsinki Declaration.

2.2. Study population

All adults (≥ 18 years old) hospitalized due to COVID-19 in the COVID-19 ward or intensive care unit (ICU) were included in this study if they had an indication for echocardiography according to "the guideline of the Iranian Society of Echocardiography for performing various types of echocardiography during the COVID-19 pandemic" (16). The indications include being in shock state or presentation of new arrhythmia (except for Premature atrial contraction (PAC) or isolated premature ventricular contraction (PVC)), cardiomegaly in the chest CT-scan, moderate or severe pericardial effusion in the chest computed tomography (CT) scan, rise of car-

diac biomarker, new or significant echocardiography (ECG) changes, generalized edema, persistent chest pain or dyspnea unexplained with pulmonary involvement, and exacerbation of the previous heart disease. COVID-19 infection was confirmed using reverse transcription-polymerase chain reaction (RT-PCR) in all cases. Pregnancy, out-of-hospital mortality, and personal request for withdrawal from the project were the exclusion criteria. After the request of cardiology consultation from the in-charge physician of the ward or ICU, if the inclusion criteria were fulfilled, echocardiography would be performed. The inclusion criteria were checked for all of the patients by an expert cardiologist. Follow-up echocardiography was performed on all of the available patients one month after discharge at the hospital cardiology clinic.

2.3. Outcomes

The primary outcome was in-hospital mortality. Study data was described in two groups of deceased and survived patients based on the in-hospital incidences. Secondary outcome was one-month follow-up changes in the echocardiographic findings, considering the vaccination as a moderator factor.

2.4. Data gathering

A checklist was developed for the purpose of gathering patients' data. Demographic characteristics (age and gender), medical history (diabetes mellitus, hypertension, ischemic heart disease, neurological disease, and cancer), and the history of COVID-19 vaccination (0-dose, 1-dose, and 2-dose) and time of vaccination were recorded on the checklist from hospital medical records initially. Patients with a history of no vaccination, 1-dose vaccination, or 2-dose vaccination in less than 2 weeks from the hospital administration against COVID-19 with any of the confirmed vaccines (by the Ministry of Health of the Islamic Republic of Iran) were considered as the not-fully vaccinated group, and patients with a history of 2-dose vaccination within two weeks or more before the hospital administration were considered the fully vaccinated group. Neither the patients nor the assessor were blinded to vaccination states.

All of the echocardiograms were performed by an expert cardiologist with more than 10 years of clinical experience in the intensive care unit (ICU). Follow-up echocardiography was performed by the same expert cardiologist. To reduce the measurement bias, an expert cardiologist who had a fellowship in echocardiography designed the study and chose the variables with the lowest dependence on the operator. Echocardiography was performed using the Vivid 3 set device (General Electric Company). All abnormalities discovered during an echocardiogram were evaluated and reported. The American Society of Echocardiography's guidelines for inter-



Table 1: Comparing the baseline characteristics of the hospitalized COVID-19 patients between survived and non-survived cases

Variable	In-hospital mortality		P
	No (n = 98)	Yes (n = 48)	
Age (year)			
Mean ± SD	60.94 ± 16.68	70.52 ± 14.10	0.002
Gender			
Male	54 (66.67)	27 (33.33)	0.89
Female	44 (67.69)	21 (32.31)	
Underlying disease			
DM	25 (59.52)	17 (40.48)	0.21
HTN	41 (65.08)	22 (34.92)	0.64
IHD	20 (58.82)	14 (41.18)	0.24
ND	6 (46.15)	7 (53.85)	0.09
Cancer	9 (60.00)	6 (40.00)	0.53
Length of hospitalization			
Mean ± SD	9.98 ± 9.07	8.08 ± 6.84	0.11
Vaccination			
No	24 (48.00)	26 (52.00)	
1 dose	24 (58.53)	17 (41.46)	<0.001
2 doses	50 (90.90)	5 (9.09)	

Data are presented as mean ± Standard Deviation (SD) or frequency (%). DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; ND: Neurologic disorders.

preparing echocardiography were followed (17). All of the categorical echocardiographic variables including cardiac valves (mitral, aortic, tricuspid, pulmonary) abnormalities (stenosis or regurgitation), high Pulmonary Artery Systolic Pressure (PASP) (≥ 35 mmHg), Left Ventricle Hypertrophy (LVH), Inferior Vena Cava (IVC) dilation, left ventricle wall motion (normal, hypokinesia, akinesia), pericardial effusion (normal, mild, moderate, severe), enlargement of ventricles (bilateral, right, left, none), Left Ventricular Systolic Dysfunction (LVSD), Left Ventricular Diastolic Dysfunction (LVDD), and Right Ventricular Systolic Dysfunction (RVSD), and also quantitative variables including left ventricle ejection fraction (%), left ventricular (LV) end-diastolic diameter (centimeter), LV end-systolic diameter (centimeter), and PASP were extracted from the echocardiographic reports.

Length of stay (days), in-hospital mortality, and ICU admission were extracted from hospital medical records after discharge of the patients. In-hospital mortality, and ICU admission were considered as prognostic factors and the main outcomes in this study.

2.5. Statistical analysis

SPSS version 25 was used for all statistical analyses. Based on the findings of Kolmogorov-Smirnov test for normality, none of the variables showed a normal distribution, so we used non-parametric tests for the analysis. Two quantitative groups were compared using Mann-Whitney U test. The association of two categorical variables was assessed using the chi-square test and, when necessary, the Fisher's exact test. Logistic regression was performed to calculate Odds ratio

(OR) of echocardiographic parameters for in-hospital mortality. The Wilcoxon signed-rank test was used to compare echocardiogram parameters at the baseline and 1-month follow-up. Statistics were considered significant for P-values under 0.05.

3. Results

3.1. Baseline characteristics of patients

146 confirmed cases of COVID-19 with the mean age of 64.09 ± 16.46 (range: 21-92) years were studied (55.5% male). The most frequent underlying diseases were hypertension (43.2%), diabetes mellitus (28.8%), ischemic heart disease (23.3%), cancer (10.3%), and neurological disorders (8.9%). The mean duration of hospitalization was 9.36 ± 8.4 days. 90 (61.6%) cases were admitted to the ICU, and also, 48 (32.9%) cases died during hospitalization. 37.7% of cases were fully vaccinated against COVID-19, 28.1% had received their first dose of vaccine, and 34.2% had not been vaccinated by the time of admission to the hospital. Baseline characteristics of the patients are described in table 1 and compared between survived and non-survived cases.

3.2. Echocardiographic findings and in-hospital mortality

The characteristics of the in-hospital echocardiograms of the studied COVID-19 patients are compared between survived and non-survived cases in table 2. There was a significant correlation between aortic valve stenosis/regurgitation ($p < 0.001$), hypokinesia in the left ventricle wall motion ($p =$



Table 2: Echocardiographic characteristics of the patients based on their mortality status

Variable	In-hospital mortality		OR (95% CI)	P
	No (n = 98)	Yes (n = 48)		
Left ventricle wall motion				
Normal	91 (70.54)	38 (29.46)	ref	-
Hypokinesia	6 (40.00)	9 (60.00)	3.59 (1.19-10.79)	0.02
Akinesia	0 (0.00)	1 (100.00)	NE	-
Mitral valve				
Normal	20 (74.07)	7 (25.93)	constant	0.43
Mild Regurgitation	71 (66.98)	35 (33.02)	1.05 (0.09-11.82)	0.567
Moderate Regurgitation	4 (44.44)	5 (55.56)	1.48 (0.15-14.74)	0.271
Stenosis	3 (75)	1 (25)	3.75 (0.27-51.37)	0.269
Tricuspid valve				
Normal	32 (69.57)	14 (30.43)	constant	0.08
Mild TR	60 (69.77)	26 (30.23)	0.27 (0.08-0.99)	0.126
Moderate/severe TR	5 (38.46)	8 (61.54)	0.27 (0.08-0.91)	0.475
Aorta valve				
Normal	88 (77.19)	26 (22.81)	ref	-
Stenosis	4 (23.53)	13 (76.47)	11 (3.3 – 36.63)	0.001
Regurgitation	6 (40)	9 (60)	2.17 (0.47-9.95)	0.32
Pulmonary Artery Systolic Pressure				
35	80 (73.39)	29 (26.61)	ref	-
≥35	18 (48.65)	19 (51.35)	2.91 (1.35-6.3)	0.001
Pericardial effusion				
No	81 (68.64)	37 (31.36)	1.37 (0.57-3.3)	0.66
Mild	16 (61.54)	10 (38.46)	NE	-
Severe	1 (100)	0 (0)	NE	-
Left Ventricle Hypertrophy				
No	74 (64.91)	40 (35.09)	0.54 (0.21-1.36)	0.2
Yes	24 (77.42)	7 (22.58)	NE	-
Inferior Vena Cava				
Normal	96 (69.06)	43 (30.94)	ref	-
Dilated	20 (38.46)	32 (61.54)	5.58 (1.04-29.41)	0.041
Enlargement of ventricles				
No	90 (66.67)	45 (33.33)	constant	0.86
Bilateral	2 (66.67)	1 (33.33)	1 (0.09-11.32)	1
LV	3 (60)	2 (40)	1.33 (0.22-8.27)	0.76
RV	3 (100)	0 (0)	NE	-
Left ventricle				
Ejection fraction, mean, SD	53.36 ± 5.75	47.28 ± 12.5	-	<0.001
End-diastolic diameter, mean, SD	5.11 ± 0.7	5.41 ± 0.75	-	0.02*
End-systolic diameter, mean, SD	3.09 ± 0.55	3.74 ± 1.31	-	<0.001
Left Ventricular Dysfunction				
Normal	79 (73.15)	29 (26.85)	ref	-
Mild systolic	3 (75)	1 (25)	0.91 (0.09-9.08)	0.94
Significant systolic	6 (33.33)	12 (66.67)	5.45 (1.87-15.86)	0.75
Mild diastolic	10 (66.67)	5 (33.33)	1.36 (0.43-4.32)	0.6
Moderate diastolic	0 (0)	1 (100)	NE	-
Right Ventricular Systolic Dysfunction				
Normal	96 (68.57)	44 (31.43)	2.59 (0.06-117.32)	0.07
Mild	0 (0)	2 (100)	NE	-
Moderate	0 (0)	1 (100)	NE	-

Data are presented as mean ± Standard Deviation (SD) or frequency (%). NE: not estimated; ref: Reference; OR: odds ratio; CI: confidence interval; TR: Tricuspid regurgitation.



Table 3: Comparing the echocardiographic parameters of COVID-19 patients at the time of admission and 1-month follow-up (F/U) between vaccinated and non-vaccinated cases

Variable	Total	P	Full vaccination	P	Incomplete vaccination	P
Left ventricle ejection fraction						
Baseline	53.27 ± 6.08	0.02	54 ± 5.09	0.28	52.56 ± 6.9	0.03
F/U	52.41 ± 5.65		53.50 ± 4.11		51.34 ± 6.71	
Left ventricle end-diastolic diameter						
Baseline	5.14 ± 0.71	0.79	5.17 ± 0.85	0.03	5.11 ± 0.57	0.11
F/U	5.14 ± 0.66		5.12 ± 0.78		5.16 ± 0.53	
Left ventricle end-systolic diameter						
Baseline	3.14 ± 0.53	0.17	3.09 ± 0.50	0.68	3.19 ± 0.55	0.11
F/U	3.16 ± 0.48		3.11 ± 0.44		3.21 ± 0.52	
Pulmonary artery systolic pressure						
Baseline	28.93 ± 7.11	0.04	28.28 ± 5.91	0.23	29.56 ± 8.13	0.93
F/U	27.93 ± 4.11		27.62 ± 4.02		28.22 ± 4.22	

Data are presented as mean ± standard deviation (SD).

0.017), higher levels of PASP (≥ 35) ($p = 0.008$), dilated IVC ($p = 0.039$), LV ejection fraction ($p = 0.00$), LV end systolic diameter ($p = 0.001$), LV end-diastolic diameter ($p = 0.018$), and left ventricular dysfunction ($p = 0.007$) with in-hospital mortality. Logistic regression analysis showed that participants with hypokinesia of the left ventricle wall had 3.59 times (95% CI: 1.19–10.79, $p = 0.02$) higher odds of mortality than participants with normal left ventricle wall motion. Also, having an aortic valve stenosis was associated with 11 times (95% CI: 3.3–36.63, $p = 0.001$) higher odds of mortality than subjects with a healthy aortic valve. A dilated IVC was associated with 5.58 times (95% CI: 1.04–29.41, $p = 0.041$) higher odds of mortality than subjects with normal IVC. Subjects with PASP ≥ 35 had 2.91 times (95% CI: 1.35–6.3, $p = 0.001$) higher odds of mortality than subjects with PASP < 35 . Data of Pulmonary valve evaluation was not included in regression due to low incidence of abnormalities (1 deceased patient with stenosis and 3 patients with regurgitation, out of which 2 died).

3.3. Follow-up echocardiography

After one month, 81 of the 98 survived cases were available for a follow-up echocardiographic evaluation. We compared some echocardiography parameters in three groups of patients: all cases, fully vaccinated, and not-fully vaccinated (table 3). LVEF decreased significantly after one month in all cases ($p = 0.02$). This decrease was not significant among patients who had a history of full vaccinations against COVID-19. Furthermore, we detected a significant decrease in LV end-diastolic diameter in the vaccinated group ($p = 0.03$) and decrease in PASP in all cases ($p = 0.004$) after one month. Although these changes were statistically significant, none of these differences are clinically important.

4. Discussion

Based on the findings of the present study, echocardiography could be considered as a useful tool for detection of high-risk COVID-19 patients. Our analysis showed that left ventricle wall hypokinesia, aorta valve stenosis, dilated IVC, and PASP ≥ 35 were associated with 3.59 (95% CI: 1.19–10.79, $p = 0.02$), 11 (95% CI: 3.3 – 36.63, $p = 0.001$), 5.58 times (95% CI: 1.04–29.41, $p = 0.041$), and 2.91 (95% CI: 1.35 – 6.3, $P=0.001$) times higher odds of in-hospital mortality.

In this study, we could find abnormalities in LV parameters in patients hospitalized due to COVID-19, which is in line with previous studies (8, 11). Direct injuries such as myocarditis due to binding of SARS-CoV-2 to ACE2 receptors or indirect injury due to shock and systematic involvement could lead to these complications (6, 18–21). Also, we could establish a significant correlation between these abnormalities and prognosis, supporting previous evidence (9, 22).

Cardiac parameters also changed in the post-infection period, especially the decrease of LVEF in patients who were not fully vaccinated. Other follow-up studies reported LV dysfunction, similar to our study (12, 14, 23). The underlying mechanisms of the post-acute phase abnormalities are not well understood. However, a long-lasting inflammatory response brought on by persisting viral reservoirs in the heart after the acute infection (24) or an immunological reaction to cardiac antigens through molecular mimicry (25) are two potential mechanisms of delayed injury.

PASP was introduced as an independent prognostic factor in the study by Pishgahi et al. (9). In this study, we found that a higher level of PASP (≥ 35) had a significant association with in-hospital mortality (2.91 times higher odds). In our follow-up, PASP decreased significantly in comparison to the baseline, supporting the findings of previous studies (13, 14). This outcome may be due to the drop in pulmonary artery pres-



sure caused by the end of the acute phase of COVID-19 and its effects on the pulmonary system (23).

Researchers are currently working hard to identify COVID-19 prediction parameters that are more reliable (26). Evidence shows that cardiovascular complications are important predictors of mortality in COVID-19 patients (27-29). A study in Iran demonstrated that EF under 30%, RV dysfunction, collapse of the IVC, and higher levels of PASP are independent factors of death in patients with COVID-19 (9). We had similar results in our logistic regression analysis. Left ventricle wall hypokinesia, aortic valve stenosis, dilated IVC, and PASP ≥ 35 were predictors of in-hospital mortality in our study.

Our study, in-line with previous studies (10, 22, 30), reported valvular dysfunction, mostly mild regurgitation of mitral and tricuspid valves. Importantly, patients with aortic valve stenosis had 11 times higher odds of mortality than patients with a normal aortic valve. The correlation between these dysfunctions and COVID-19 is still vague, but they are likely related to a previously diagnosed or undiscovered disease or ventricular dilatation (8). They are not the/considered an exact indication for echocardiography, but we suppose they should be. They could be diagnosed with an exact auscultation of the heart and then referred to echocardiography. Like in previous studies (11, 22, 30, 31), mild pericardial effusion (PE) was a common finding in our study, but we could not establish a significant correlation between PE and the prognosis of patients.

It has been established that vaccination can prevent severe COVID-19 cases, hospitalization, and mortality (32). Yet more research is needed to fully understand its capacity to prevent secondary complications like cardiac complications. In the follow-up phase, we could only find a significant decrease in LVEF in non-fully vaccinated patients. Non-fully vaccinated patients might experience a different compensatory pattern of cardiac recovery than vaccinated patients; further long-term follow-ups are needed to investigate this matter. In-line with our study, a recent study in South Korea revealed that full vaccination against COVID-19 is correlated with a lower risk of acute myocardial infarction following COVID-19 infection (33).

5. Limitation

There are some limitations in our study that should be mentioned. In this study, we only included patients hospitalized due to COVID-19. Therefore, our inclusion criteria would limit the generalizability of the results to patients with moderate or severe diseases that need hospitalization. Echocardiography is an operator-dependent tool and a potential source of bias. However, to reduce the measurement bias, an expert cardiologist who had a fellowship in echocardiography designed the study and chose the variables with the

lowest dependence on the operator. Also, all of the echocardiograms were performed with the same device model and by the same person. Echocardiograms were performed on different days of hospitalization, and changes in echocardiograms on different days are unclear. We performed follow-up echocardiograms only one month after discharge. Further studies to evaluate serial changes in echocardiograms after COVID-19 infection are recommended.

6. Conclusion

Left ventricle wall hypokinesia, aorta valve stenosis, dilated IVC, and PASP ≥ 35 were predictors of in-hospital mortality in our study. While we did not see any potential clinically significant differences in one-month echocardiographic follow-ups of our patients, non-fully vaccinated patients might experience a different compensatory pattern of cardiac recovery than vaccinated patients; yet, further long-term follow-ups are needed.

7. Declarations

7.1. Acknowledgments

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7.2. Author contribution

Study design and data gathering: All of authors.

Analysis: SMMA

Interpreting the results: All of authors

Drafting: SMMA, SHM

Critically revised: SHM, MK, AA, RA, AM

All authors read and approved the final version of the paper to be submitted.

7.3. Conflict of interest

The authors declare no conflict of interest.

7.4. Data Availability

The datasets created and analyzed during the current study are accessible upon reasonable request from the corresponding author.

7.5. Funding

None.



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