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Incidence of Persistent Symptom and Echocardiographic Findings in Survivors of COVID–19 Infection with Mild Symptoms

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Abstract

Background: In patients who survived COVID-19 infection. Multi-organ and mechanisms of disease can be involved. The data regarding echocardiographic dimension and function of the cardiac in the COVID-19 survivors remains scarce.

Methods: This was a descriptive cross-sectional study that involves a total of 63 subjects. Subjects were employees and medical residents at National Cardiovascular Center Harapan Kita, who previously get infected by COVID-19. Each subject was examined transthoracic echocardiography once at the time of recruitment. Echocardiographic parameters obtained in this study included dimension and systolic function of the left ventricle and right ventricle, global longitudinal strain by 2D speckle tracking echocardiography, and myocardial work index.

Results: More than a half of the subjects experienced persistent symptoms after recovery from COVID-19 infection and mainly was fatigue (33.3%). The timing of data acquisition on the median was 32 days after the negative of the COVID-19 test result. 2D echocardiography measurement of left ventricle indicated mean of end-diastolic diameter and end-systolic diameter was 45 mm and 27 mm, respectively. The mean ejection fraction (EF) of the left ventricle by Simpson's biplane method was 61%. The median of tricuspid annular plane systolic excursion (TAPSE) parameter was 23 mm and fractional area change (FAC) parameter was 39%. The mean of global longitudinal strain (GLS) was -19.6%.

Conclusion: After recovery from COVID-19 infection, some survivors may have post-acute infectious consequences of COVID-19 such as fatigue, dyspnea, and malaise. However, echocardiographic findings in those patients with mild symptoms, including 2D echocardiography, myocardial strain analysis, and myocardial work index, indicate normal dimension and systolic function in both left ventricle and right ventricle.

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Keywords: post-covid syndrome, symptom sequelae, echocardiography.

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Introduction

COVID-19 infection is a global pandemic affecting many countries over the world.[1] Morbidity and mortality consequences of the pandemic are yet high and vaccination efforts lately offer very high expectancy. On the other hand, the number of patients who recover from the infection are increasing.

In addition to prevention and treatment, one of the necessary actions to overcome the impact of the pandemic is rehabilitation after suffering COVID-19 infection. In patients who survived COVID-19 infection, some patients yet have residual symptoms such as shortness of breath, fatigue, and headache.[2] Multi-organ and mechanisms of disease can be involved in persistent symptoms after COVID-19 infection. SARS-CoV-2 infection affecting the cardiovascular system and caused the myocardial injury.[3] How significant and how long the impact on the survivor is yet little known.

Methods

This was a descriptive cross-sectional study that involves a total of 63 subjects. Subjects were employees and medical residents at National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. Subjects were recruited consecutively. Inclusion criteria in this study were subjects aged 18 – 75 years old and have ever been infected with COVID-19, confirmed by PCR test result. Whereas, exclusion criteria were subjects who have a history of coronary heart disease, cardiomyopathy, valvular disease, congenital heart disease, arrhythmia, and heart failure.

Data regarding personal identity, past medical history, family history, and course of COVID-19 infection were collected with the questionnaire. Blood pressure and heart rate were measured at the time of recruitment. Each subject was examined transthoracic echocardiography once at the time of recruitment. This study was approved by the ethical committee at National Cardiovascular Center Harapan Kita, and all of the subjects informed consent before recruitment.

Transthoracic echocardiography examination was performed using GE Vivid E9 and E95 cardiovascular ultrasound machine. Operators were practiced cardiologists and cardiovascular technicians at National Cardiovascular Center Harapan Kita echocardiography laboratory. Acquisition of image and measurement refers to Cardiac Chamber Quantification guidelines from the American Society of Echocardiography (ASE).[4] Echocardiographic parameters obtained in this study included dimension and systolic function of the left ventricle (LV) and right ventricle (RV), global longitudinal strain (GLS) by 2D speckle tracking echocardiography, and global myocardial work index. Echocardiographic data were collected and analyzed at ViewPoint 6 software (GE healthcare).

Automated Functional Imaging (AFI) was used for evaluation of 2D strain. Speckle-tracking analysis of the LV was carried out in three apical views (4-chamber, 3-chamber, and-2 chamber). The automatic tracking of the endocardial border came up with software was manually validated. Myocardial work analysis was carried out using ViewPoint6. After calculation of global longitudinal strain, measurement of brachial blood pressure were filled in, and the time of cardiac cycle events was determined by software.

Statistical analysis was performed using SPSS 25 version software. Numerical data were presented as mean ± standard deviation if data is normally distributed and as median ± range if data is not normally distributed. The categorical variable was presented as a percentage.

Results

The total subjects recruited were 63 people included 49 medical healthcare (77.8%) and 14 non-medical healthcare. Most of them (62%) were hospitalized in the ward, while the rest was self-isolation. All of the subjects have mild symptoms, and none required the intensive care unit. Echocardiography was performed at four days to 289 days, median 32 days, after the negative PCR test result. All of the subjects in this study have not been vaccinated before infection.

As shown in **Table 1**, all of the subjects were symptomatic at the time of COVID-19 infection and for the most part, were fatigue and headache in the amount of 48%. More than a half of the subjects (50.8%) experienced persistent symptoms after recovery from COVID-19 infection and mainly was fatigue.

Table 1. Characteristic of the subjects.

Variable		n (%)
Age (years)		37 (25-58)
Gender	Male	23 (36.5%)
	Female	40 (63.5%)
Comorbid		
	Hypertension	14 (22.2%)
	Diabetes	2 (3.2%)
	Mellitus	4 (6.3%)
	Smoker	5 (7.9%)
	Dyslipidemia	0 (0%)
	Chronic kidney	0 (0%)
	disease	0 (0%)
	Liver disease	0 (0%)
	Heart disease	
	Lung disease	
Symptom during infection		
	Fever	41 (65%)
	Dry cough	27 (42.8%)
	Fatigue	48 (68.6%)
	Muscle pain	45 (76.2%)
	Dysphagia	21 (33.3%)
	Diarrhea	16 (25.4%)
	Red eye	11 (17.4%)
	Headache	48 (76.2%)
	Anosmia	30 (47.6%)
	Skin lesion	8 (12.7%)
	Dyspnea	19 (30.1%)
	Chest pain	9 (14.3%)
Symptom sequelae		
	Fatigue	21 (33.3%)
	Dyspnea	7 (11.1%)
	Malaise	4 (6%)
	Myalgia	2 (3.2%)
	Headache	2 (3.2%)
	Dry cough	1 (1.6%)
	Anosmia	1 (1.6%)
Duration of infection (days)		27 (9 - 95)
Negative of the COVID-19 test period (days)		32 (4 - 289)

One subject has mild RV dilatation. Five subjects have low RV-free wall strain values (>-19%). Three subjects have low global longitudinal strain values (>-17%). The results of echocardiography measurement are shown in **Table 2**. Comparison of echocardiography findings in patients with and without persistent symptoms are shown in **Table 3**

Discussion

To our knowledge, this study is the first descriptive study in Indonesia that revealed echocardiographic findings in the COVID-19 survivors with persistent symptoms. The survivors of COVID-19 experience some symptoms sequelae which is called post-acute COVID-19 syndrome. Post-acute COVID-19 syndrome is characterized by persistent symptoms and or long-term complications after COVID-19 infection.[3]

All of the subjects were only experience mild symptoms when COVID-19 infected them. Those results could be because the mean age of subjects in this study is young. COVID-19 showed a lower risk of severe disease with decreasing age.[5] In this study, there were half of the subjects experience persistent symptoms. These persistent symptoms have been associated with several variables. The study by Harpin et al. exhibits an association between pre-existing respiratory disease, higher body mass index, older age, and dyspnea at 4-8 weeks follow-up.[6]

Recent literature reported that survivors of COVID-19 have a symptom that mimics post-viral syndrome such as fatigue, chronic malaise, myalgia, and headache.[7] Moreover, other symptoms such as loss of taste and smell are reported persistent in one-tenth until 6 months follow-up.[8] The post-acute-COVID-19 US study showed that dyspnea is the most reported symptom by the survivors with the amount of 22.9%. The post-acute-COVID-19 Italian studies reported survivors felt fatigued at the most with the amount of 53.1%.[9] These were in concordance with this study which showed the incidence of fatigue was 48%, being the most commonly reported symptom.

Fatigue and dyspnea after COVID-19 infection can be caused by multi-organ, included cardiac. Echocardiography examination is one modality that can be used to evaluate that matter. Although, current evidence does not support the use of echocardiography for routine evaluation of COVID-19 survivors.[10]

Based on normal reference values from the guidelines, the mean of the dimension and function of both LV and RV are within normal limits.[4, 11] Likewise, the mean of LV global longitudinal strain and RV free wall strain measured by speckle tracking echocardiography, indicate normal value. The global longitudinal strain has been proven could exhibit subclinical cardiac dysfunction.[12]

Table 2. Physical examination and echocardiographic findings.

Variable		
Physical examination		
	Systolic blood pressure (mmHg)	120 (103-160)
	Diastolic blood pressure (mmHg)	78 (59-110)
	Heart rate (beat/minutes)	75 ± 9.3
	Height (cm)	160 (145-185)
	Weight (kg)	71 ± 12.9
	Body mass index (kg/m2)	27 ± 4.2
	Body surface area (m2)	1.7 ± 0.18
Comorbid		
	Hypertension	14 (22.2%)
	Diabetes Mellitus	2 (3.2%)
	Smoker	4 (6.3%)
	Dyslipidemia	5 (7.9%)
	Chronic kidney disease	0 (0%)
	Liver disease	0 (0%)
	Heart disease	0 (0%)
	Lung disease	0 (0%)
2D Echocardiography of LV		
	LV end diastolic diameter (mm)	45 ± 4.4
	LV end systolic diameter (mm)	27 ± 4.0
	IVS diastolic diameter (mm)	9 (6 - 14)
	IVS systolic diameter (mm)	12 (8 - 18)
	LV posterior wall diastolic diameter (mm)	9 (5 - 13)
	LV posterior wall systolic diameter (mm)	13 (8 - 17)
	End diastolic volume (Simpson's bi-plane)	92 ± 22
	End systolic volume (Simpson's bi-plane)	36 ± 11
	Ejection fraction (Simpson's bi-plane)	61 ± 7
2D Echocardiography of RV		
	RVOT diameter PLAX (mm)	29 ± 3.7
	RVOT diameter proximal (mm)	29 ± 4.5
	RVOT diameter distal (mm)	20 ± 3.5
	RV basal diameter (mm)	36 ± 5.3
	RV mid diameter (mm)	26 ± 4.6
	RV longitudinal diameter (mm)	67 (21 - 83)
	RV end diastolic area (mm)	17 ± 4.5
	RV end systolic area (mm)	10 (4 - 21)
	FAC (%)	39 (24 - 62)
	TAPSE (mm)	23 (19 - 28)
Global longitudinal strain (GLS) and Myocardial Work (MW)		
	Global work index (GWI) (mmHg%)	1782 ± 244
	Global constructive work (GCW) (mmHg%)	2108 ± 315
	Global wasted work (GWW) (mmHg%)	91 (30 - 250)
	Global work efficiency (GWE) (mmHg%)	95 (84 - 98)
	LV global longitudinal strain (%)	-19.6 ± 2.1
	RV Free Wall strain (%)	-25.8 ± 4.9

Note: LV = left ventricle; RV = right ventricle; IVS = interventricular septum; RVOT = right ventricle outflow tract; FAC = fractional area changes; TAPSE = tricuspid annular plane systolic excursion; GLS = global longitudinal strain; MW = myocardial work; GWI = global work index; GCW = global constructive work; GWW = global wasted work; GWE = global work efficiency.

Table 3. Echocardiographic findings in patients with and without persistent symptom.

	Persistent symptom	Without persistent symptom	P-value
2D Echocardiography of LV			
LV end diastolic diameter (mm)	45 ± 4.0	45 ± 4.0	0.19
LV end systolic diameter (mm)	28 ± 3.9	27 ± 4.2	0.44
IVS diastolic diameter (mm)	9 (6 - 14)	9 (6 - 14)	0.53
IVS systolic diameter (mm)	9 (6 - 13)	10 (7 - 14)	0.72
LV posterior wall diastolic diameter (mm)	9 (5 - 12)	9 (6 - 13)	0.34
LV posterior wall systolic diameter (mm)	13 (9 - 16)	13 (8 - 17)	0.15
Ejection fraction (Simpson's bi-plane)	61 ± 5	62 ± 8	0.57
2D Echocardiography of RV			
RVOT diameter PLAX (mm)	30 ± 4.0	29 ± 3.5	0.19
RVOT diameter proximal (mm)	29 ± 4.9	29 ± 4.1	0.71
RVOT diameter distal (mm)	20 ± 3.9	20 ± 3.1	0.66
RV basal diameter (mm)	37 ± 5.5	36 ± 5.1	0.29
RV mid diameter (mm)	24 ± 5.1	26 ± 4.1	0.84
RV longitudinal diameter (mm)	66 ± 9.8	66 ± 6.0	0.84
RV end diastolic area (mm)	17 ± 4.9	17 ± 4.1	0.71
RV end systolic area (mm)	10 (4 - 21)	10 (6 - 16)	0.70
FAC (%)	38 (24 - 53)	40 (29 - 62)	0.71
TAPSE (mm)	23 (19 - 28)	23 (19 - 28)	0.89
Global longitudinal strain (GLS) and Myocardial Work (MW)			
Global work index (GWI) (mmHg%)	1799 ± 280	1764 ± 203	0.57
Global constructive work (GCW) (mmHg%)	2098 ± 363	2108 ± 315	0.80
Global wasted work (GWW) (mmHg%)	91 (32 - 250)	94 (30 - 224)	0.90
Global work efficiency (GWE) (mmHg%)	94 (84 - 98)	95 (89 - 98)	0.49
LV global longitudinal strain (%)	19.9 ± 2.3	19.4 ± 1.9	0.64
RV Free Wall strain (%)	26.1 ± 5.6	25.5 ± 4.2	0.47

Note: LV = left ventricle; RV = right ventricle; IVS = interventricular septum; RVOT = right ventricle outflow tract; FAC = fractional area changes; TAPSE = tricuspid annular plane systolic excursion; GLS = global longitudinal strain; MW = myocardial work; GWI = global work index; GCW = global constructive work; GWW = global wasted work; GWE = global work efficiency.

However, the global longitudinal strain has limitations that do not include afterload into the analysis.

Global myocardial work index is the novel noninvasive method for getting the measure of myocardial performance. This method is using global longitudinal strain data integrate with noninvasive blood pressure measurement for generating cardiac performance in the shape of a pressure-strain loop. The global myocardial work index is including afterload as of the result more accurately for evaluating myocardial performance.[11] Therefore, this study also acquired global myocardial work index data.

Based on normal reference values from the EACVI NORRE study, myocardial work analysis was not affected after COVID-19 infection.[11] In this study, meanwhile, there were 22.2% of subjects who have hypertension. As opposed to a prior study conducted by Tadic et al.[13], which indicates significantly deteriorated global myocardial index in hypertensive patients, the global myocardial index in those subjects was in the normal range. These can be caused by different mean of blood pressure at the time of measurement, which indicates hypertension in this study is more controlled than the previous study, 125 ± 17 mmHg versus 147 ± 11 mmHg, respectively.[13]

Based on current literature, mechanisms that can contribute to persistent symptoms are cellular damage, inflammatory cytokine production, and pro-coagulation state induced by SARS-CoV infection.[14] Data from cardiac Magnetic Resonance Imaging (MRI) elegantly showed that there is still myocardial inflammation more than two months after infection. Still, the study did not evaluate its correlation with the symptom.[15]

Unlike cardiac sequelae, the manifestation of lung sequelae, both radiological and functional, is more evident. COVID-19 survivors have restrictive pulmonary physiology at three months and six months after infection.[16] Furthermore, a systematic

review suggested that about half of the patients with COVID-19 still had residual abnormalities on chest CT and pulmonary function test at about three months.[17] In this study, we did not examine lung function. Perhaps, this phenomenon is also applied in our subjects.

This study showed that there is no difference in echocardiography findings between patients with and without persistent symptoms. This study's cross-sectional category does not allow approximation and explanation of the causal association between persistent symptoms with cardiac function. The subjects have mild symptoms and without significant complications during the infection period. We could only hypothesize that the persistence of symptoms is not related to impaired LV and RV systolic function in this type of survivor.

The results of this study bring pertinent recognition of the dimension and systolic function of the left and right ventricle after COVID-19 infection. The long-term outcome of cardiovascular sequelae after COVID-19 infection is little known. Further systematic studies are needed to reveal the causality, mechanism, evaluation, follow-up, treatment, and prognosis of cardiovascular sequelae after COVID-19 infection.

Conclusion

After recovery from COVID-19 infection, some survivors may have post-acute infectious consequences of COVID-19 such as fatigue, dyspnea, and malaise. However, echocardiographic findings in those patients with mild symptoms, including 2D echocardiography, myocardial strain analysis, and myocardial work index, indicate normal dimension and systolic function in both left ventricle and right ventricle.

Ethical Clearance

Ethical clearance for this study was approved and issued by Institutional Ethical Review Board of National Cardiovascular Center Harapan Kita

Publication Approval

All authors read and approved final version of manuscript

Conflict of Interest

None

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